

## Ca Patient's 'Unexplained' Fever Laid to Infection

Medical Tribune Report

WASHINGTON—Unsuspected and difficult to diagnose infection, often of fungal etiology, may explain "unexplained" fever in cancer patients, investigators from the Division of Infectious Diseases at Indiana University School of Medicine, Indianapolis, told the 15th Interscience Conference on Antimicrobial Agents and Chemotherapy sponsored by the American Society for Microbiology.

Important clues to the presence of infection are the type of neoplasm, the granulocyte count and clinical or laboratory abnormalities indicating specific organ involvement, they suggested.

"While many neoplasms are capable of causing fever without the presence

of infection, cancer patients often have compromised immune mechanisms, either by virtue of their disease or because of therapeutic agents used in treatment, which tend to make them more susceptible to opportunistic infections," said Dr. Friedrich C. Luft, head of the research team.

### Patient Acutely Ill

He and Drs. J. Petr Rissing, Arthur White, and Geo. F. Brooks, evaluated the causes of fever of unexplained origin (FUO) in 36 cancer patients seen during a 30-month period. Sixteen patients had lymphoma, 12 leukemia, and eight solid tumors.

Each patient met certain criteria: a diagnosis of malignant neoplasm docu-

mented prior to fever onset; fever of at least three weeks duration; fever higher than 38.3 degrees centigrade on several occasions; and an uncertain diagnosis after one week in hospital.

"These criteria served to exclude patients with fever due to self-limited viral infections and those with bacterial infections responsive to antimicrobial therapy," Dr. Luft explained. "These patients were acutely ill. They had persistent fever in spite of antimicrobial therapy with combinations of antibiotics which included gentamicin, cephalothin and carbenicillin."

The research team anticipated that the majority of patients selected would prove to have fever secondary to neoplasms. "This did not occur," declared

Dr. Luft. "Minimally, 50 per cent of our patients had infections. And it was not possible to rule out the presence of infection with absolute certainty in patients who had fevers presumably due to their neoplasms."

Fungi were the cause of infection in nine of the 18 infected patients. Histoplasmosis was found in three patients, candidiasis in three and aspergillosis, systemic sporotrichosis and cryptococcal meningitis in one patient each.

"This reflects the increasing importance of fungi as a source of infection in patients with compromised body defenses," noted Dr. Luft.

Six patients had unresolved pyogenic infections, one had tuberculous peritonitis, and two had viral infections.

In the 18 apparently noninfected patients, fever appeared associated with some change in the neoplasm, according to Dr. Luft. "Five of the six patients with solid tumors had noted new masses or swellings and lymphoma patients often had newly enlarged lymph nodes," he said.

While the infected and noninfected groups of patients had a number of features in common, for example age and sex distribution and mean duration of fever, several distinguishing parameters were noted.

"Absolute granulocyte counts were strikingly different for the two groups," said Dr. Luft. "In infected patients, marked granulocytopenia was evident. Eleven patients in this group had absolute granulocyte counts of less than 1000/mm<sup>3</sup> and five others less than 3000/mm<sup>3</sup>."

"In contrast, few of the noninfected patients had granulocytopenia. Only one patient in this group had a granulocyte count of less than 1000/mm<sup>3</sup>."

Type of neoplasm also distinguished infected from noninfected patients, according to Dr. Luft. All 12 leukemia patients had infection.

### Morphologic Exams

Morphologic examination of biopsy or aspirate specimens, with cultures, was the most productive diagnostic measure, the research team concluded.

"In infected patients, likely sites for productive biopsy procedures were clinically apparent. These included pulmonary infiltrates visible on chest roentgenograms or abnormalities detected on physical examination. There was a paucity of abnormalities indicating organ system involvement with infection in the other 18 patients."

"Regardless, physicians' diagnostic efforts should not be deterred in such patients," Dr. Luft continued. "Repeated thorough evaluations for infection are warranted."

Dr. Luft stressed, however, that diagnostic measures must be tailored to the individual cancer patient. Noting that a large number of aggressive procedures were done in the apparently noninfected patients, he said: "These patients were able to withstand major diagnostic efforts whereas the often moribund infected patients could not. In the latter instances, the physician and patient together must decide whether surgical diagnostic procedures and potentially toxic antimicrobial therapy will prolong useful life or make dying difficult."

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Wednesday, November 14, 1973

## Is the Administration Taking Research Control From NIH?

By KEN SANILER

Medical Tribune Staff

WASHINGTON—A secret meeting of two former secretaries of the Department of Health, Education, and Welfare, a former head of the National Institutes of Health, the president of the National Academy of Sciences, a former U.S. Surgeon General, the deans of three major medical schools, and prominent researchers, was convened here to discuss the implications of allegations that the Nixon Administration is taking control of the NIH's biomedical research out of the hands of the researchers and physicians and transferring it to lawyers and politicians within the Administration—and is firing government scientists who oppose the new policy.

The group has asked the National Academy of Sciences to conduct an investigation of this alleged removal of research policy decisions from the scientists, and reliable sources close to Sen. Abraham Ribicoff (D-Conn.) stated that he will hold open hearings—at which NIH officials will be called on to testify—on the Government's research policies within the next few months.

Scholars at NIH, the Food and Drug Administration's Bureau of Biologics, and other officials confirmed, in discussions with Medical Tribune, some of the charges that morale has been wrecked by the Nixon policies. Because of the delicacy of the situation ("criticize the Administration, and you'll be looking for a new job"), Medical Tribune agreed to not-for-attribution interviews.

Participants at the meeting, which was informally sponsored by Senator Ribicoff, himself a former Secretary of HEW, included Wilbur J. Cohen, another former HEW Secretary, now dean of the School of Education at the University of California at Berkeley. Continued on page 20

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SEN. A. RIBICOFF

### Patient's Clot Helps Stop Bleeding



Dr. Joseph Bookstein, a radiologist from the University of Michigan, has developed a technique for using a modified clot of the patient's own blood and placing it in a damaged artery to control internal bleeding (see story, page 13). Left, light spot (at arrow) on angiogram shows puddling from lesion in left gastric artery. Bleeding persisted despite transcatheter hemostasis with vasopressors. A 1-cc. clot was treated with thrombin and forced through the catheter. Angiogram a few minutes later (right) shows absence of lesion. Control was essentially permanent, since no rebleeding occurred.

## Hormone Test Aids in Choice Of Therapy for Breast Tumor

Medical Tribune Report

SAN DIEGO, CALIF.—A 24-hour in vitro assay, which indicates that about half of all breast tumors depend on one or more hormones for their growth, is now helping clinicians decide whether a mastectomy is necessary or whether the tumor growth can be suppressed by drug therapy or by surgical techniques.

Dr. John R. Hobbs, of the Tumor Biology Group, Westminster Hospital Group, London, told a seminar at the Scripps Clinic here.

In the test, a slice of tumor tissue is incubated for 24 hours in medium containing prolactin or some other hormone and compared with a similar slice incubated without the hormone in the same medium. If tumor tissue growth depends on the hormone, the effect can be detected visually or by an increase in the activity of the cancer-related enzyme, dehydrogenase, he explained.

Clinical experience indicates that five patients with tumors shown to be prolactin-dependent in the test underwent periods of regression when the pituitary was removed, Dr. Hobbs stated, explaining that the pituitary gland controls the production of prolactin. In other cases when prolactin levels returned to normal after the removal of the pituitary, the Sandoz drug CB-154 reduced prolactin and also caused a positive regression of the breast tumor. This drug (2-bromo-ergocryptine) is not yet available in the United States.

Similarly, in nine of 10 patients whose breast cancers were shown in the test to depend on estrogen, positive regression was observed when their ovaries were removed or when they were treated with testosterone or antiestrogen drugs.

In five patients whose tumors were dependent on androgen, as seen in the test, adrenalectomy or treatment with an anti-androgen drug caused regression in four.

The test now indicates that there are at least five types of hormone-dependent breast tumors. They include those that depend on prolactin only, prolactin and estrogen, prolactin and testosterone, testosterone only, and estrogen only.

"Where combined dependence is present, the results are more complex," Dr. Hobbs explained.

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## Atherosclerosis May Signify Return to Lobsterlike State

Medical Tribune Report

BETHESDA, Md.—Atherosclerosis in man may be caused by the reversion of his arterial wall to an evolutionary primitive state similar to that of the arterial wall of the lobster, says Solomon Laki, Ph.D., of the National Institute of Arteriosclerosis.

## Britain's NHS at 25

PART II

By NATHAN HORWITZ

Medical Tribune Staff

Britain's comprehensive health care program was in near disarray by the mid-'60s. Physician discontent was at a peak, the "brain drain" was in full swing, and even Continental advocates of national health insurance were pointing to Britain as a good example of how not to do it. How the British worked their way out of the mess is told in this second of a series of articles on the National Health Service.

LONDON—As Britain's National Health Service moves into its second quarter-century, the nation's 23,000 general practitioners are a good deal less tired than they were a few years ago.

They also are better paid, more assured of themselves, and gaining immeasurably in public esteem and professional status.

A recent national survey showed that 91 per cent of patients questioned were satisfied with the health care they were getting. The criticisms of 9 per cent were leveled largely at problems of hospital service and admissions for elective procedures.

Another sign of the times is that general practice is increasingly a specialty of choice among medical students. And still another is that Britain's medical schools now have eight chairs of general practice or family practice. Two years ago there were none.

This is a far cry from the picture in the early '60s, when British G.P.s, along with other physicians, were emigrating to Canada, Australia, and the United States.

"That was a period," recalled Dr. Donald Irvine, secretary of the Royal College of General Practitioners, "when going into general practice meant going into a dead-end street."



DR. DENNIS COOK

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## Institute Plagued by Money Problems



Prof. Jacques Monod, left, director of the Pasteur Institute.

## Lack of Funds Forces Pasteur to Cut Staff

Medical Tribune World Service

PARIS—Threatened by dwindling funds and a straitened budget, the 85-year-old Pasteur Institute announced that it will cut its 1,120-member staff by a little over 10 per cent; between 125 and 135 people will soon be facing dismissal.

"It is a question of maintaining the institute in existence or shutting down," its director, Prof. Jacques Monod, said.

The institute was originally established as an antirabies center in November, 1888, three years after nine-year-old Joseph Meister became the first patient bitten by a rabid dog to receive the 10-day series of immunizations developed by Louis Pasteur. In the wake of the success of the immunization, 2,500 victims of rabid bites underwent therapy.

Donations to establish the institute came from people all over the world, including the czar of Russia, the sultan of Turkey, and the emperor of Brazil. Its dedication, which came two years after Pasteur had received the Reynard Prize for his work on rabies, was attended by the president of France and other notables.

At present the institute receives an-



Reynard Archive Photos

nual research subsidies from the French Government that amount to about 15,000,000 francs. Between 1970 and 1973, however, payroll costs alone rose from 23,000,000 to 34,000,000 francs, with an accompanying personnel increase of only 70, Professor Monod said.

He is hoping for subsidy increases that, when added to the proposed pay-

roll saving, would give the institute an additional 10,000,000 francs a year and its continuing independence. He emphasized that foreseen staff cuts would take place only in what he called "the lesser disciplines," and reaffirmed top priorities for the institute's research in microbiology, immunology, fundamental biochemistry, and molecular biology.

## Penicillin-Group Drugs Still Most Popular Antibiotics

Medical Tribune World Service

ATHENS—Drugs of the penicillin group and those related to it are still used almost as often as all other antibiotics combined, according to an analysis of prescribing practices relating to more than 15,000 hospital patients in three countries. Tetracyclines and cephalosporins stand in second and third place, and gentamicin is increasingly more popular than kanamycin. Chloramphenicol has not been used since 1971.

Reporting these data from the Boston Collaborative Drug Surveillance Program, which groups nine hospitals in the United States, Canada, and Israel, Dr. J. Borda told the eighth International Congress of Chemotherapy here that adverse reactions were most often gastrointestinal.

Ampicillin, neomycin, and tetracycline were incriminated in about two-thirds of the GI reactions, most of which were mild or moderate.

Dr. Borda, of the University of Western Ontario, London, Ont., commented: "Nausea, vomiting, diarrhea, anorexia, and such symptoms are notoriously difficult to evaluate in sick people. They cannot be 'measured,' neither can the possibility of a placebo effect be ignored."

More than one-half of the skin reactions were attributed to the penicillin-ampicillin group. Ampicillin was held responsible 101 times; the penicillins, although more often used, only 57 times. Kanamycin, gentamicin, neomycin, and tetracycline were related to most of the renal effects. Relatively few hematologic reactions were recorded.

Four deaths were attributed to antibiotics. Superinfection had developed in three of the four cases. In two it was a gram-negative septicemia and in the third a massive necrotizing pneumonia due to *Candida albicans*. Concomitant steroid treatment was given to two of these patients.

The fourth death was due to renal failure in a patient who had received

prolonged kanamycin and gentamicin therapy.

"Four deaths in close to 10,000 patients treated with antibiotics, a rate of one in every 2,500, is relatively few," Dr. Borda observed. "Nevertheless, it reinforces the concept that chemotherapy treatment be given with specific indications, restricted to necessary drugs, and special attention be paid to concomitant steroid administration."

Dr. Borda also reported that three types of serious drug-induced events—convulsions, deafness, and anaphylaxis—have recently been studied in the program.

Among 12,617 patients, drug-attributed convulsions occurred in 17 (1.3 per 1,000). Out of 1,245 patients given intravenous penicillin, four had convulsions (3.2 per 1,000). None of the patients had epilepsy or other diseases affecting the central nervous system.

## New Radioactive Agent May Enable Nonsurgical Detection of Metastases

Medical Tribune Report

CHICAGO—Preliminary results from a study of 75 cancer patients scanned after receiving a new radioactive pharmaceutical, bleomycin tagged with indium-111, offer promise of a nonsurgical means for accurate staging and earlier detection of subclinical metastatic disease.

Excellent correlation with proven diagnosis was obtained in 59 patients (79 per cent accuracy) with primary metastatic melanomas, carcinomas, sarcomas, and lymphomas, according to Dr. Melvin J. Silverstein, director of the Multidisciplinary Breast Clinic, University of California, Los Angeles.

The accuracy rate, reportedly greater than in existing scanning methods, appears to be similar in an additional 75

patients not included in the study because of insufficient follow-up.

"In cases we have studied, concentration in the tumor is five to 25 times greater than in normal skeletal muscle," Dr. Silverstein reported. "What we need is the hardware to pick up that concentration. Once we get better scanning equipment, we hope to get tumors smaller than 2 cm, tumors not now adequately scanned with existing equipment."

Labeled bleomycin, an antineoplastic antibiotic, concentrates in tumor to a much higher degree than labeled gallium, which is currently used.

The reason for localization is not known, said Dr. Silverstein, but may be related to the inflammatory reaction and the edema.

## news index

CLINICAL NEWS NOTE: "Excessive intake of preformed vitamin A has resulted in serious toxic side effects, especially in young children, and there is considerable documentation to support this statement" (Dr. Arnold P. Gold; see "Current Opinions," page 6.)

Medicine: pgs. 1, 2, 3, 4, 5, 6, 10, 11, 13, 20, 21, 26, 28, 32

Mandatory relicense for physicians is predicted within the next 10 years with specialty recertification also due.

Common preservatives found to inhibit growth and cause morphologic changes in human cells

Internal bleeding may be arrested by plugging the vessel with a modified clot from patient's own blood, a variation of transcatheter thrombolysis

Ob/Gyn: pgs. 12, 19

Monthly antifertility drug that blocks the production of specific reproductive hormones will be tested by a team of Salk investigators

Pediatrics: pgs. 7, 11, 31

Unlabeled foreign objects in the esophagus may produce respiratory symptoms that fool diagnosticians

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Dimethylhydrazine, the immediate precursor of choline, is found to retard the aging process of mice

Lung transplant feasibility is shown in animal tests in which lungs that were removed and then replaced had virtually normal structure and function

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Stone heart has been prevented by prophylactic use of hypothermia during cardiac surgery

Bypass surgery for impending myocardial infarction results in increased mortality in patients with four or more hemodynamic risk factors

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## Smoke of Burning Synthetic Carpet Held Lethal Hazard

Medical Tribune Report

CHICAGO—Animal experiments showing the death-dealing potential of smoke produced by flaming acrylic and nylon carpeting were reported here by a Harvard Medical School investigator, who urged that standards of biologic tolerance be established for synthetic fibers.

Tests of flammability are not adequate, Dr. Donald P. Dressler told the Clinical Congress of the American College of Surgeons.

Rats invariably die—often in less than two minutes—after inhaling smoke from ignited acrylic carpeting at a temperature otherwise compatible with survival.

Dr. Dressler pointed out that synthetic fibers, such as acrylic, are now replacing wool in carpeting in schools, commercial buildings, and homes.

Emphasizing that smoke inhalation accounts for more than 5,000 deaths each year, he said the studies he conducted jointly with Drs. Edna Britanney and Anne W. Phillips "clearly demonstrate that indiscriminate use of building and decorating materials may result in lethal hazards."

## 750 Rats Exposed to Smoke

In the experiments, some 750 rats were exposed in a controlled-atmosphere chamber to smoke produced by standard acrylic rugs, wool rugs, or white pine wood. Temperature and humidity as well as smoke concentrations could be controlled and monitored.

Each type of material was either ignited or allowed to smolder in a combustion chamber. The smoke produced was cooled or heated as desired and then introduced into the animal chamber at a rate of 40 cubic feet per minute.

Smoke from smoldering material, whatever its source, caused no deaths if inhaled at room temperature, Dr. Dressler said. As could be expected, he added, the higher the temperatures, the greater the mortality, and mortality increased with length of exposure at any given temperature.

But tests made of smoke from ignited—rather than smoldering—materials revealed that the acrylic carpeting was deadly even at room temperature (25° C., 77° F.). All animals inhaling such smoke at this temperature died, and they frequently did so within two minutes. Later tests showed that nylon carpeting appeared to be "even more dangerous on ignition," according to Dr. Dressler.

By comparison, smoke from ignited

wood or ignited wool carpeting caused no deaths during the test period in the chamber at the same temperature of 25° C.

In an interview with MEDICAL TRIBUNE, Dr. Dressler commented that solid data are lacking on the part played by building and decorative materials in the smoke inhalation deaths resulting from such disasters as airplane crashes and fires in offices, houses, or nursing homes.

What the animal studies indicate, he said, is that the chances for escape and survival are good if a person is exposed only to smoke produced by smoldering, provided the temperature remains fairly cool.

"But if synthetic fibers like acrylic are ignited, you're in trouble," he continued. "The 'escape time' for a rat is one or two minutes. We don't know about the human being—it's hard to extrapolate from animal to man—but certainly the margin of safety is small once the material is ignited."

## Degu Has 2 Thymuses



The degu, a ratlike rodent found in the lower altitudes of the Andes Mountains of South America, possesses an unusual biologic quirk—it has two anatomically separate thymus glands. Because of this, Dr. David Boraker, an immunologist at the University of Vermont, is developing a pedigreed colony for biologic experimentation.

## NIAID Test Shows Level of Antibody To Mycoplasma

Medical Tribune Report

BETHESDA, Md.—A new test for detection of antibody to *Mycoplasma pneumoniae*, the organism responsible for outbreaks of acute respiratory infection during late summer and early fall, has been developed by Drs. Robert M. Chanock, chief of the Laboratory of Infectious Diseases of the National Institute of Allergy and Infectious Diseases, and Helmut Brunner, according to NIAID.

The test utilizes a modified radioimmuno-precipitation procedure in which small amounts of radioactively labeled mycoplasma antigen are incubated with serum being tested for antibody. Anti-human gamma globulin or whole serum, prepared in animals, is then added to precipitate the antigen-antibody complex and, after overnight incubation, the material is centrifuged.

The amount of radioactivity in the precipitate indicates the amount of antigen bound to specific antibody and the presence or lack of antibody in the serum sample, the investigators said.



## Bobo's back at the big top

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## New Percutaneous Technique Effective for Biliary Relief

Medical Tribune World Service

MONTREAL—A new technique of percutaneous transhepatic biliary decompression may be the best method for patients whose pending liver failure or over-all condition makes it impossible to reconstruct the biliary tree.

Drs. Alfred E. Stockum and William Molnar, of the Department of Radiology, University Hospitals, Ohio State University, reported that they have now used the percutaneous technique in 10 patients over the past four years. In certain well-selected cases, transhepatic biliary decompression is "the only remedy to improve the desperate condition of the patient," they told the American Roentgen Ray Society here.

Obstructive jaundice, if caused by stricture of the common duct, is usually from surgical trauma, they said. "The subsequent, multiple surgical interventions, including possible primary repair and choledochal or hepatic anastomosis to intestinal tract, all may yield to occasional stenosis causing recurrent ascending cholangitis and chronic hepatitis. Uncontrollable pruritus, psychosis,

and occasional portal hypertension may further aggravate the clinical condition, which eventually ends in hepatic failure and coma."

### Retarded for Cholangiography

Drs. Stockum and Molnar pointed out that all 10 of their patients were originally referred to them for visualization of the biliary structures by percutaneous cholangiography. Five had benign stenosis, and five had obstruction caused by malignant tumor. After they visualized the biliary system and decided on percutaneous drainage, they inserted under local anesthesia an 18-gauge, thin-walled needle sheathed with a Teflon catheter through the ninth intercostal space at the midaxillary line. They then directed the needle into a free, contrast-filled tributary of the right hepatic duct, and brought a curved-tip guide wire through the needle; it was then advanced into either the left duct or an adjoining right duct tributary. The needle was then removed and, using the guide wire, the number 7 Teflon catheter was manipulated into its final position. "The catheter

in this position will provide external biliary drainage which will be collected into a plastic bag attached to the catheter. Direct internal drainage is established only if the tube can be guided across the stenotic, compressed, or invaginated segment into the unobstructed intestinal loop or distal common duct."

In their first patient, they recalled, "the transhepatic drainage tube was inserted with the intention only to improve the patient's condition before the contemplated surgical intervention three weeks later. In the rest of the patients the demonstrated condition of the biliary system precluded further surgical intervention."

Detailing the indication for use of the percutaneous drainage technique, they cited four benign conditions in which it could prove of value: postoperative common duct stricture; restenosed choledochoduodenal or jejunal anastomosis; intrahepatic biliary stones, where the procedure may allow direct irrigation through the tube utilizing heparin or bile salt solutions to dissolve the stones; and sclerosing cholangitis without renal failure.

A second group of indications include intrahepatic obstruction caused by primary or metastatic tumors and recurrent extrahepatic obstruction due to primary biliary or pancreatic tumors.

## Blood Substitute Said to Fulfill 5 Out of 6 Criteria

Medical Tribune Report

CHICAGO—Stroma-free hemoglobin solution, made from outdated human whole blood, has been used successfully to maintain a puppy for one hour during heart-lung bypass.

The performance of the solution was similar to that of whole blood, according to Dr. Wilfred F. Holdrege, of the Department of Surgery, University of Alabama.

"Our data suggest the possible effectiveness of stroma-free hemoglobin solution as a whole-blood substitute," he reported to the Clinical Congress of the American College of Surgeons.

He said it fulfills five of the six criteria of an ideal blood substitute: There is no generalized or allergic reactions due to antibody-antigen sensitivity. There is no interference with typing and cross-matching of blood and no adverse effect on body organs.

However, the solution cannot now be retained in the blood system for an effective period. It is excreted rapidly by the kidneys.

"The next step is a chemical problem," said Dr. Holdrege. "Since this is a chemical solution—there are no cells in it—it may be possible to hook the hemoglobin onto a molecule that would not be readily excreted."

In isolated heart perfusion, the performance of the hemoglobin solution in oxygen transport was also similar to that of whole blood.

The absence of tissue reactions as a result of species differences suggests that animal blood may be one day used where large quantities are required.

### Bleeding Reported in Tests With Blood Substitute

Hektoen Institute Investigator

A group from Hektoen Institute for Medical Research, Chicago, reported that the use of stroma-free hemoglobin was accompanied by severe bleeding in experimental animals because it apparently destroyed factor VIII and, to a lesser extent, factor V.

An anticoagulant has been identified and can be purified and synthesized, according to Alan Cochin, associate director of the surgical research department. "The synthetic peptide, closely related to the natural anticoagulant, might be of value in treating abnormal clot formation."

## Impure Anesthetic Causes Infections

Medical Tribune Report

BETHESDA, Md.—The use of a nonsterile hyp water in the preparation of topical anesthetics for an ear, nose, and throat clinic caused an outbreak of respiratory tract infections at Vanderbilt University Hospital, Nashville, Tenn., the National Institute of Allergy and Infectious Diseases (NIAID) reported.

The isolation of the contaminant organism, *Pseudomonas cepacia*, in bronchial washings from 22 patients, 18 of whom had been treated in the ENT clinic, spurred an investigation by a team headed by Dr. William Schaffner.

### ECTOPIC BEAT

"The suicide prevention centers opened in recent years to major cities across the nation have failed to make much of a dent in the suicide rate."

—release from the A.M.A. And that's the way it goes, these days.

(Regular beat, *Immature Maturity*, page 38)

## Specialty Recertification Also Due

Medical Tribune Report

CHICAGO—Within the next 10 years physicians will be required to be relicensed to practice medicine and to be recertified to practice as specialists, the new president of the American College of Surgeons, Dr. Claude E. Welch, told that body.

"Patient care will continue to be available to the public at several levels in the future just as it is today," Dr. Welch said, "but . . . the optimum care of the present time can be improved even more by yet untested mechanisms. Recertification and relicensure furnish important methods that must be considered in detail."

Relicensure and recertification, Dr. Welch said, "certainly are not pleasing to the practicing surgeon, who visualizes another noose around his neck and further depletion of his rare hours of leisure."

"It is not a pleasant prospect for the young physician, whose admission to medical school essentially guaranteed graduation, often without marks or examinations. Nor is it complimentary to the medical profession to receive this unique criticism. But there is overwhelming evidence that this will occur. In the vernacular, it is a new ball game."

He noted that it is an issue on which the American College of Physicians has taken an official stand, and that his own remarks bore no official endorsement.

But he added, "I believe it is imperative that the college immediately investigate the entire subject of recertification and relicensure; thereafter, if the college declares itself in favor of these procedures, it must plan for the tactics of its involvement."

"Multiple Pathways" Urged

As for what position the college should take, Dr. Welch said, "My recommendation would be that it approve multiple pathways to recertification, that strong support be given to outcome evaluation, and that any attempt to require examinations as a sole method for recertification be opposed."

As of now, Dr. Welch said, six state medical societies require evidence of continuing postgraduate education for continuation of membership, and 13 others have recommended voluntary participation.

The American Board of Medical Specialties last March called for the voluntary, periodic recertification of medical specialists. It is likely that "real teeth" will be inserted in these recommendations when the words "voluntary" and "certification" are replaced by "mandatory" and "licensure," Dr. Welch said.

"At the present time," he said, "recertification can be regarded as a merit badge—a nice decoration to wear but of no economic significance. In the future, if relicensure is based on recertification, it could become a matter of economic life or death."

There are several ways recertification can be accomplished, he said. The first and easiest would be a simple re-examination by computer every five to 10 years. The penalties for the 10 to 20 per cent that might be expected to fail would range from mild to severe, perhaps from a warning to required attendance at postgraduate courses to exclusion from practice until a further examination is passed.

"It is obvious that this method could be cruel to the individual and catastrophic to the community in which he practices," said Dr. Welch. "Nevertheless, this method, because of its facility, is the most likely to be chosen."

A second method of recertification would be individual participation in a variety of educational activities, including attendance at clinical congresses, meetings of other specialty societies, or participation in other academic pursuits.

A third method would be a peer review system in which a surgeon's record would be considered as the basis of recertification. "Undoubtedly deficiencies in practice would be found," said Dr.

Welch. "Some surgeons have changed to become general practitioners, with insufficient surgical experience to maintain their skills. A few may be entangled in problems of ethics. In general, however, it is likely that few black sheep will be found among our members."

The third method, affirming that "nothing succeeds like success," avoids the valid criticism that a good mark on an examination does not equate with surgical ability, said Dr. Welch.

On the subject of relicensure, Dr. Welch said some measure of government control would be "almost inevitable."

"The state already has difficult decisions to make when it defines various health professions. Let it continue to focus on this level and describe the differences, for example, between a physician, a dentist, a nurse, or a podiatrist. At the higher level, licensure of specialists should not be done unilaterally by the state," he said.

The benefits to the public of recertification and relicensure would include well-trained physicians who continually

renew their knowledge, Dr. Welch said. Specialists would not be required to restrict their practice to their specialty. A specialist could continue to function as a primary physician, but a surgeon would be expected to offer the highest quality care only in his specialty.

### Operations Will Remain

"Emergency surgery in isolated communities will remain, and 'elective surgery, even in the hands of relatively untrained men, will persist," he said.

Dr. Welch noted that the Massachusetts Chapter of the College of Surgeons, after considering the factors that improve the performance of a surgeon, suggested that such factors should add to the basic fee for a given service. Under this system, a general practitioner would be paid the basic fee for a surgical service.

Additions to the fee would also be allowed if (1) the surgeon were board-certified, (2) he were a member of the American College of Surgeons, (3) he had at least five years experience as a practicing surgeon, and (4) he could prove continuing education in surgery.

## 'Bioplate' Perfected



Medical investigators at Stanford University have perfected a "bioplate" to be inserted into a patient's jugular vein and threaded into his heart to obtain a small sample of cardiac tissue. It is used to make direct diagnosis of rejection in heart transplants.

Before prescribing or administering, see Sandoz literature for full product information. The following is a brief summary.

Contraindications: Severe central nervous system depression, comatose states from any cause, hypersensitive or hypotensive heart disease of extreme degree.

Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when the potential benefits exceed the possible risks to mother and fetus.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving) and increase dosage judiciously. Orthostatic hypotension is more common in females than in males. Do not use apomorphine in treating drug-induced hypotension since phenothiazines may induce a re-

versed apomorphine effect on occasion. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.

Adverse Reactions: Central Nervous System—Drowsiness, especially with large doses, easily in treatment; incontinently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperreflexia, lathargy, psychotic reactions, restlessness, and headache. Autonomic Nervous System—Dryness of mouth, blurred vision, constipation, nausea, vomiting, claudication, nasal stuffiness, and pallor. Endocrine System—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. Skin—Dermatitis and skin eruptions of the urticarial type, photosensitivity. Cardiovascular System—ECG changes (see Cardiovascular Effects below). Other—A single case described as parotid swelling.

The following reactions have occurred with phenothiazines and should be considered: Autonomic Reactions—Miosis, constipation, anorexia, paralytic ileus. Cutaneous Reactions—Erythema, exfoliative dermatitis, contact dermatitis. Blood Dyscrasias—Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia. Allergic Reactions—Fever, laryngeal edema, angioedema, anaphylaxis, asthma. Hepatotoxicity—Jaundice, biliary stasis. Cardiovascular Effects—Changes in terminal portion of electrocardiogram, including prolongation of Q-T interval, lowering and inversion of T-wave, and appearance of a wave tentatively identified as a third T or a U wave have been observed with phenothiazines, including Mellaril (thioridazine); these appear to be reversible and due to altered repolarization, not myocardial damage. While there is no evidence of a causal relationship between these changes and significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients showing characteristic electrocardiographic changes while taking the drug. While proposed, periodic electrocardiograms are not regarded as predictive. Hypotension, rarely resulting in cardiac arrest. Extrapyramidal Symptoms—Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, and skiasia. Persistent Tardive Dyskinesia—Persistent and sometimes irreversible involuntary dyskinesia, characterized by rhythmic involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, pulling of cheeks, puckering of mouth, chewing movements) and sometimes of extremities may occur on long-term therapy or after discontinuation of therapy, the risk being greater in elderly patients on high-dose therapy, especially females; if symptoms appear, discontinue all antipsychotic agents. Syndrome may be masked if treatment is reinstituted, dosage is increased, or antipsychotic agent is switched. Fine vermicular movements of tongue may be an early sign, and syndrome may not develop if medication is stopped at that time. Endocrine Disturbances—Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema, false positive pregnancy tests. Urinary Disturbances—Retention, incontinence. Dehydration—Hyperpyrexia, behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states; following long-term treatment, a peculiar skin-eye syndrome marked by progressive pigmentation of skin on conjunctiva and/or accompanied by discoloration of exposed sclera and cornea, stellate or irregular opacities of anterior lens and cornea.

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## High Concentrations of Vitamin A

By ARNOLD P. GOLD, M.D.

Associate Clinical Professor of Neurology (Pediatrics)  
College of Physicians and Surgeons  
Columbia University, New York, N.Y.

DR. LINUS PAULING'S STATEMENT criticizing the limitation of nonprescription sale of vitamin A tablets and capsules containing more than 10,000 International Units, which was sent to Dr. Charles E. Edwards, FDA commissioner, and made available to MEDICAL TRIBUNE, published on February 28, requires comment. The statement is replete with inaccuracies necessitating a response in view of Dr. Pauling's eminence as a professor of chemistry and twice recipient of the Nobel Prize. The views and opinions of Dr. Pauling may in part be attributed to his theoretical chemical background rather than to the practice of clinical medicine.

The American Academy of Pediatrics Committee on Drugs, in conjunction with the Committee on Nutrition, formulated a joint committee statement entitled "The Use and Abuse of Vitamin A." This commentary noted the potential grave risks relative to unrestricted sale of high concentrations of vitamin A and urged restrictions be placed on over-the-counter marketing of high-potency vitamin A preparations. This factual presentation contributed to the FDA proposal to restrict the over-the-counter sale of vitamin A to tablets and capsules containing more than 10,000 International Units.

The recommended daily allowance of vitamin A is: for infants and children up to the age of 12 years, 1,500 to 4,500 I.U.; for adults, 5,000 I.U.; and for pregnant women, 6,000 I.U. There are no known advantages in exceeding these allowances in normal individuals, and the limitations on over-the-counter sale to products exceeding 10,000 I.U. of vitamin A seem reasonable to protect the American people, above all children, from the toxic effects of excessive vitamin A intake. Dr. Pauling certainly presents no evidence for his recommended optimum daily intake of 25,000 I.U. of vitamin A.

EXCESSIVE INTAKE of preformed vitamin A has resulted in serious toxic side effects, especially to young children, and there is considerable documentation to support this statement. High doses of vitamin A taken for prolonged periods of time pose a risk, particularly to the pregnant woman and fetus. In pregnant animals large doses of vitamin A can produce central nervous system anomalies resulting in hydrocephalus or encephalocele in the offspring. Infants may develop a clinical picture of hydrocephalus, while the older child and adult with hypervitaminosis A manifest signs and symptoms of uncalculated intracranial pressure, which is often referred to as the pseudotumor cerebri syndrome. Children frequently present with signs and symptoms such as headaches, nausea, vomiting, lethargy, irritability, diplopia, papilledema with hemorrhages, and, in long-standing cases, optic atrophy and even blindness can result. There are many other nonspecific findings encountered at all ages with excessive vitamin A intake, including dry skin and mucous membranes, sparse hair, brittle nails, myalgia, bone pain, arthralgia, abdominal pain, splenomegaly, and hypoplastic anemia with leukopenia. For these reasons the validity of the FDA regulation is apparent and is necessary to protect the

### Sri Lanka Health Data

Medical Tribune World Service

COLOMBO—Government medical institutions have been supplying "unreliable and at times false" data on infectious diseases, the Sri Lanka department of epidemiology charged.

As a result, said the head of the department, Dr. Reginald Peiris, a correct assessment of the country's health situation cannot be made.

and rare to find daily ingestion of half a pound of animal liver. For this reason there would be no indication to restrict the sale of such foods.

Although many people may ingest potentially toxic doses of vitamin A over long periods of time without developing hypervitaminosis A, the major factor is that some people—above all, unsuspecting children—may and have developed clinical hypervitaminosis A.

In no way does the FDA regulation restrict the prescription of high doses of vitamin A when there is a medical indication for its use, such as in nutritional deficiency states or in a state of chronic intestinal malabsorption. What the regulation does restrict is the over-the-counter sale in drugstores and supermarkets of high dosage preparations, for the easy availability and indiscriminate usage expose both children and adults to the hazards of this potential poison.

I do believe that the practicing physician should be alerted to the problem of hypervitaminosis A and that a review of the available factual data will aid him in critically reviewing such statements as that of Dr. Pauling's as well as clarifying the logic and intent of the FDA regulation.

American people from hypervitaminosis A.

I fail to understand Dr. Pauling's statement that the regulation would be largely ineffective and would be economically damaging to the public.

Dr. Pauling's comments relative to the vitamin A content of certain foods are pertinent as further indication for limitation of the vitamin A content in over-the-counter sales. The daily intake of supplemental vitamins is commonly employed by a significant segment of the population, while it would be uncommon

## What the Sleep Research Laboratory recorded about DALMANE<sup>®</sup> sleep...<sup>1</sup>

(flurazepam HCl)

- reduced sleep latency
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- increased total sleep time

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Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

**Indications:** 1. To promote sleep in patients with insomnia. 2. To promote sleep in patients with anxiety. 3. To promote sleep in patients with depression. 4. To promote sleep in patients with chronic pain. 5. To promote sleep in patients with chronic cough. 6. To promote sleep in patients with chronic asthma. 7. To promote sleep in patients with chronic heart disease. 8. To promote sleep in patients with chronic kidney disease. 9. To promote sleep in patients with chronic liver disease. 10. To promote sleep in patients with chronic lung disease. 11. To promote sleep in patients with chronic neurological disease. 12. To promote sleep in patients with chronic psychiatric disease. 13. To promote sleep in patients with chronic reproductive disease. 14. To promote sleep in patients with chronic skin disease. 15. To promote sleep in patients with chronic systemic disease.

**Contraindications:** Known hypersensitivity to flurazepam HCl or any of its components.

**Warnings:** 1. Patients should be warned of the potential for dependence and addiction. 2. Patients should be warned of the potential for abuse. 3. Patients should be warned of the potential for tolerance. 4. Patients should be warned of the potential for withdrawal. 5. Patients should be warned of the potential for impaired judgment and coordination. 6. Patients should be warned of the potential for impaired driving. 7. Patients should be warned of the potential for impaired operation of machinery. 8. Patients should be warned of the potential for impaired social behavior. 9. Patients should be warned of the potential for impaired academic performance. 10. Patients should be warned of the potential for impaired athletic performance. 11. Patients should be warned of the potential for impaired work performance. 12. Patients should be warned of the potential for impaired family life. 13. Patients should be warned of the potential for impaired social life. 14. Patients should be warned of the potential for impaired personal life. 15. Patients should be warned of the potential for impaired overall health.

**Precautions:** 1. Patients should be warned of the potential for dependence and addiction. 2. Patients should be warned of the potential for abuse. 3. Patients should be warned of the potential for tolerance. 4. Patients should be warned of the potential for withdrawal. 5. Patients should be warned of the potential for impaired judgment and coordination. 6. Patients should be warned of the potential for impaired driving. 7. Patients should be warned of the potential for impaired operation of machinery. 8. Patients should be warned of the potential for impaired social behavior. 9. Patients should be warned of the potential for impaired academic performance. 10. Patients should be warned of the potential for impaired athletic performance. 11. Patients should be warned of the potential for impaired work performance. 12. Patients should be warned of the potential for impaired family life. 13. Patients should be warned of the potential for impaired social life. 14. Patients should be warned of the potential for impaired personal life. 15. Patients should be warned of the potential for impaired overall health.

**Adverse Reactions:** 1. Drowsiness. 2. Headache. 3. Nausea. 4. Vomiting. 5. Constipation. 6. Dry mouth. 7. Blurred vision. 8. Impaired judgment. 9. Impaired coordination. 10. Impaired driving. 11. Impaired operation of machinery. 12. Impaired social behavior. 13. Impaired academic performance. 14. Impaired athletic performance. 15. Impaired work performance. 16. Impaired family life. 17. Impaired social life. 18. Impaired personal life. 19. Impaired overall health.

**Dosage:** 1. 30-mg capsule h.s. 2. 15-mg capsule h.s. 3. 10-mg capsule h.s. 4. 5-mg capsule h.s. 5. 2.5-mg capsule h.s. 6. 1.25-mg capsule h.s. 7. 0.625-mg capsule h.s. 8. 0.3125-mg capsule h.s. 9. 0.15625-mg capsule h.s. 10. 0.078125-mg capsule h.s. 11. 0.0390625-mg capsule h.s. 12. 0.01953125-mg capsule h.s. 13. 0.009765625-mg capsule h.s. 14. 0.0048828125-mg capsule h.s. 15. 0.00244140625-mg capsule h.s. 16. 0.001220703125-mg capsule h.s. 17. 0.0006103515625-mg capsule h.s. 18. 0.00030517578125-mg capsule h.s. 19. 0.000152587890625-mg capsule h.s. 20. 0.0000762939453125-mg capsule h.s. 21. 0.00003814697265625-mg capsule h.s. 22. 0.000019073486328125-mg capsule h.s. 23. 0.0000095367431640625-mg capsule h.s. 24. 0.00000476837158203125-mg capsule h.s. 25. 0.000002384185791015625-mg capsule h.s. 26. 0.0000011920928955078125-mg capsule h.s. 27. 0.00000059604644775390625-mg capsule h.s. 28. 0.000000298023223876953125-mg capsule h.s. 29. 0.0000001490116119384765625-mg capsule h.s. 30. 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## Barbiturate Use As Anesthetic May Cut Stroke

Medical Tribune Report

ATLANTIC CITY, N.J.—Clinical trials of barbiturates as the anesthetic or anesthetic supplement in surgery that poses a high risk of brain infarction were advocated here by investigators from the University of California School of Medicine, San Francisco, and Stanford University School of Medicine.

Their studies of dogs in which cerebral artery occlusion was experimentally produced have demonstrated that inclusion of barbiturate in the anesthetic regimen prevented strokes, the research team told the 46th Scientific Sessions of the American Heart Association.

In the laboratory trials, the right internal carotid and middle cerebral arteries were permanently clipped through a temporal burr hole in 42 dogs, divided according to anesthetic management into seven groups of six animals.

Four groups received halothane anesthesia, categorized as light, "awake" (the agent discontinued three minutes before vessel occlusion), deep, and deep with hypotension (equal increased five minutes before vessel clipping to reduce mean arterial blood pressure to 55 torr).

Of the remaining three groups, one had deep pentobarbital anesthesia, another received light halothane plus thiopental begun just before cerebral artery occlusion, and the third was given light halothane plus thiopental begun 15 minutes after occlusion.

### Protective Action Clear

Findings from daily neurologic examinations as well as from brain pathology studies performed when the animals were killed on the seventh day clearly indicated the protective action of barbiturates, the investigators reported.

No neurologic abnormalities occurred in the six dogs that received deep pentobarbital anesthesia and only one of the 12 animals given thiopental before or after vessel occlusion had a neurologic deficit—a transient unilateral weakness.

By contrast, hemiparesis occurred in five of six animals in both the light and "awake" halothane groups. In the deep halothane groups, all the normotensive dogs and five of the six hypotensive animals became severely hemiplegic.

The brain studies also revealed significant differences between the barbiturate and nonbarbiturate groups in mean infarction size.

In the three barbiturate groups, means of less than 3 per cent of the right hemisphere were infarcted. Mean infarction size for the other groups was much greater: "awake" halothane, 9.6 per cent; light halothane, 10.8 per cent; deep halothane normotensive, 28.2 per cent; deep halothane hypotensive, 34.1 per cent.

"We believe that barbiturates protect principally by decreasing cerebral blood flow and intracranial pressure," the investigators said.

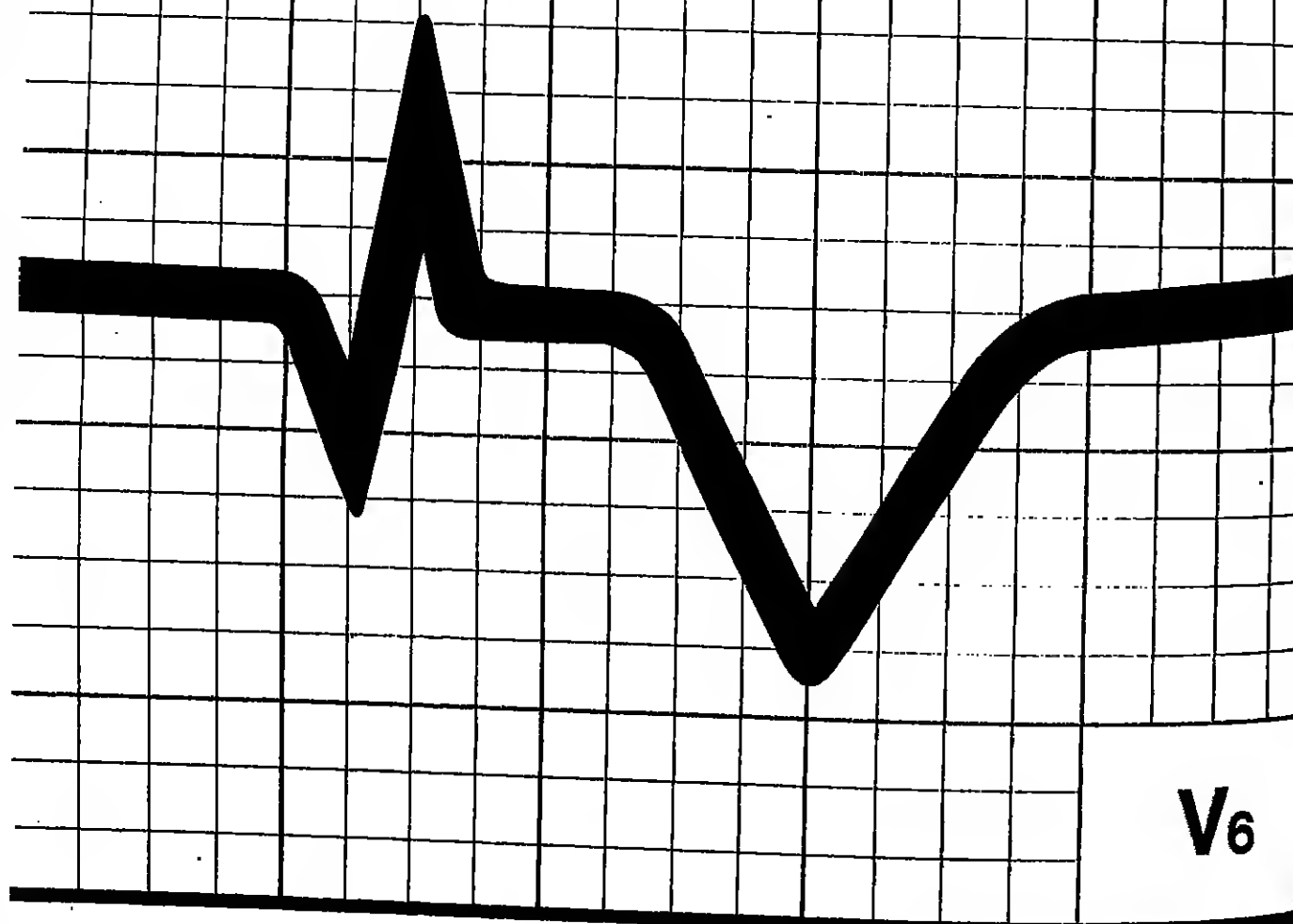
"The lowered intracranial pressure would minimize pressure in cerebral capillaries and venules, thus maximizing perfusion pressure in ischemic areas. . . . The low cerebral blood flow of barbiturate anesthesia would minimize cerebral edema, and might reduce capillary stasis and/or capillary damage."

Noting that increasing numbers of patients with cerebrovascular disease are subjected to corrective surgical procedures, the report pointed out that the risk of brain damage is high because of the temporary or permanent occlusion of cerebral vessels required by carotid artery thromboendarterectomy, cerebral aneurysm ligation, and cerebral artery bypass.

The investigators concluded that clinical trials of such barbiturates as thiopental are warranted for these procedures and suggested that barbiturates should perhaps be considered for treatment of acute stroke.

Members of the research team were Drs. Allen L. Smith, Julian T. Hoff, Surl L. Nielsen, and C. Philip Larson.

## Tranxene® (CLORAZEPATE DIPOPOSSUM) won't solve the organic problems of your heart patients



In three dosage strengths: 3.75 mg. 7.5 mg. 15 mg.

Dosage and Administration: Orally, in divided doses; usually daily dose is 30 mg. Dose should be adjusted gradually within range of 15 to 60 mg. daily. In elderly or debilitated patients, it is advisable to initiate therapy at a daily dose of 7.5 mg. to 15 mg.

**DESCRIPTION:** Chemically, TRANXENE (clorazepate dipotassium) is a benzodiazepine. The empirical formula is  $C_{15}H_{10}Cl_2N_2O_4$ ; the molecular weight is 408.33. The compound occurs as a fine, light yellow, practically odorless powder. It is insoluble in the common organic solvents, but very soluble in water. Aqueous solutions are unstable, clear, light yellow, and alkaline.

**ACTIONS:** Pharmacologically, TRANXENE (clorazepate dipotassium) has the characteristics of the benzodiazepines. It has depressant effects on the central nervous system. The primary metabolite, nordiazepam, reaches peak level in the blood stream at approximately 1 hour. The plasma half-life is about 1 day. The drug is metabolized in the liver and excreted primarily in the urine. (See ANIMAL AND CLINICAL PHARMACOLOGY section).

**INDICATIONS:** TRANXENE is indicated for the symptomatic relief of anxiety associated with anxiety neurosis, in other psychoneuroses in which anxiety symptoms are prominent features, and as an adjunct in disease states in which anxiety is manifested.

**CONTRAINDICATIONS:** TRANXENE (clorazepate dipotassium) is contraindicated in patients with a known hypersensitivity to the drug, and in those with acute narrow angle glaucoma.

**WARNINGS:** TRANXENE is not recommended for use in patients with a history of depression or in depressive neurosis or in psychotic reactions.

Patients on TRANXENE should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating dangerous machinery including motor vehicles.

Since TRANXENE has a central nervous system depressant effect, patients should be advised against the simultaneous use of other CNS-depressant drugs, and cautioned that the effects of alcohol may be increased.

Because of the lack of sufficient clinical experience, TRANXENE (clorazepate dipotassium) is not recommended for use in patients less than 18 years of age.

**Physical and Psychological Dependence:** Withdrawal symptoms (anxiety, tremor, headache, muscle aches, and insomnia) have occurred in those treated with barbiturate and alcohol. In those treated with TRANXENE, withdrawal symptoms have not occurred following abrupt discontinuance of clorazepate. Symptoms of nervousness, insomnia, irritability, diarrhea, muscle aches, and memory impairment have followed abrupt withdrawal after long-term use of high dosage.

Caution should be observed in patients who are considered to have a psychological potential for drug dependence.

Evidence of drug dependence has been observed in dogs and rabbits which was characterized by convulsive seizures when the drug was abruptly withdrawn or the dose was reduced; the syndrome in dogs could be abolished by administration of clorazepate.

**Usage in Pregnancy:** Reproduction studies have been performed in rats and rabbits and there was no evidence of harm to the animal fetus. The relevance to the human is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established.

It is assumed that TRANXENE or its metabolites are excreted in human milk. Therefore, this drug should not be given to nursing mothers.

**PRECAUTIONS:** In those patients in which a degree of depression accompanies the anxiety, suicidal tendencies may be present and protective measures may be required. The least amount of drug that is feasible should be available to the patient.

In elderly or debilitated patients, the initial dose should be small, and increments should be made gradually, in accordance with the response of the patient, to produce anxiolysis or sedation.

**ADVERSE REACTIONS:** This side effect most frequently reported was drowsiness. Less commonly reported (in descending order of occurrence) were dizziness, various gastrointestinal complaints, nervousness, blurred vision, dry mouth, headache, and mental confusion. Other side effects included insomnia, tran-

## But it can help relieve excessive anxiety without clouding the symptom picture

Consider.

In controlled, double-blind studies, Tranxene . . .

- showed no adverse effect on pulse rate (no bradycardia reported)
- showed no effect on blood pressure, other than a lowering of slightly elevated systolic pressure in some patients
- produced no drug alterations in ECG in the two studies where electrocardiographic effects were investigated
- produced no serious side effects at recommended doses. The most commonly seen side effects were drowsiness, lightheadedness and gastrointestinal complaints

Tranxene contains no sodium; potassium content is minimal. Use with caution in patients who are considered to have a potential for drug abuse.



sis, skin rashes, fatigue, dizziness, genito-urinary complaints, irritability, diplopia, depression and slurred speech.

There have been reports of abnormal liver and kidney function tests and of decrease in hematocrit.

Progress to systolic blood pressure has been observed.

**DOSE AND ADMINISTRATION:** TRANXENE (clorazepate dipotassium) is administered orally in divided doses. The usual daily dose is 30 mg. The dose should be adjusted gradually within the range of 15 to 60 mg. daily in accordance with the response of the patient. Drowsiness may occur at the initiation of treatment and with dosage increments. In elderly or debilitated patients it is advisable to initiate treatment at a daily dose of 7.5 to 15 mg.

**DRUG INTERACTIONS:** TRANXENE (clorazepate dipotassium) is to be combined with other drugs acting on the central nervous system, careful consideration should be given to the pharmacology of the agent to be employed. Animal experience indicates that TRANXENE, by prolonging the sleeping time after heavy doses of chlorpromazine, but does not exhibit marked sedation with concurrent hypnotic medication. TRANXENE is used to treat anxiety associated with various disease states, careful attention must be paid to possible drug interaction with concomitant medications.

**MANAGEMENT OF OVERDOSEAGE:** As in the management of overdose with any drug, it should be borne in mind that multiple agents may have been

taken. If vomiting has not occurred spontaneously, it should be induced. Immediate gastric lavage is also recommended. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated. Hypotension, through untimely or excessive use of vasopressor (diazepam) or vasopressor (metaraminol), Caffeine and Sodium Benzoate Injection, U.S.P. may be used to counteract central nervous system depressant effects.

There has been reported a 41-year-old woman who took 75 capsules (1875 mg.) of TRANXENE. Severe diarrhea and vomiting occurred, but she made an uneventful recovery without being hospitalized.

**ANIMAL AND CLINICAL PHARMACOLOGY:** Studies in rats and monkeys have shown a substantial difference between doses producing tranquilizing, sedative and toxic effects. In rats, conditioned avoidance response was inhibited at an oral dose of 10 mg. kg.; sedation was induced at 32 mg. kg. The LD<sub>50</sub> was 1320 mg. kg. In monkeys aggressive behavior was reduced at the oral dose of 0.25 mg. kg.; sedation (ataxia) was induced at 7.5 mg. kg.; the LD<sub>50</sub> could not be determined because of the emetic effect of large doses, but the LD<sub>50</sub> exceeds 1600 mg. kg.

Twenty-four dogs were given TRANXENE orally in a 22-month toxicity study; doses up to 75 mg. kg. were given. Drug-related changes occurred in the liver; weight was increased and cholesterol with minimal hepatocellular damage was found, but tubular architecture remained well preserved.

Eighteen rhesus monkeys were given oral doses of TRANXENE from 3 to 36 mg. kg. daily for 52 weeks. All treated animals remained healthy and gained weight. Although total leukocyte count remained within normal limits, a few leukocytes were found in the femoral marrow in the highest doses.

Examination of all organs revealed no alterations attributable to TRANXENE. There was no damage to liver function or structure.

**Reproduction Studies:** Standard studies of fertility, teratology and reproduction were conducted on rats and rabbits. Oral doses in rats up to 150 mg. kg. and in rabbits up to 15 mg. kg. produced no abnormalities in the fetuses and no impairment to fertility and reproductive capacity of adult animals attributable to TRANXENE (clorazepate dipotassium). An expected, sedative effect of high doses interfered with care of the young by their mothers (see Use in Pregnancy).

**Clinical Pharmacology:** Studies in healthy men have shown that TRANXENE has depressant effects on the central nervous system. Prolonged administration of high doses (120 mg. daily as a single oral dose) was without toxic effects, and abrupt cessation of drug was not followed by serious signs or symptoms.

**Absorption—Excretion:** After oral administration of TRANXENE (clorazepate dipotassium), there is essentially no circulating parent drug. Nordiazepam, its primary metabolite, quickly appears in the blood stream with peak levels at about 1 hour. The plasma half-life is approximately 1 day. In 2 volunteers given 15 mg. (50 µg.) of <sup>14</sup>C-TRANXENE, about 80% was recovered in the urine and feces within 18 days. Excretion was primarily in the urine with about 1% excreted per day on day 10.

**HOW SUPPLIED:** TRANXENE (clorazepate dipotassium) is supplied as capsules in three dosage strengths: 3.75 mg. capsules (gray with white cap) in bottles of 100 (NDC 074-3417-13) and 500 (NDC 074-3417-53); 7.5 mg. capsules (gray with maroon cap) in bottles of 100 (NDC 074-3418-13) and 500 (NDC 074-3418-53); 15 mg. capsules (all gray) in bottles of 100 (NDC 074-3419-13) and 500 (NDC 074-3419-53).

## Compound Found That Influences Process of Aging

Medical Tribune Report

CORONA DEL MAR, CALIF.—The immediate precursor of choline, dimethylaminoethanol (DMAE), a compound synthesized in minute quantities by human beings and found in all living organisms, may retard aging process, according to Richard Hochschild, of the Microwave Instruments Company here.

Mr. Hochschild said that DMAE acts as a stabilizer on the lysosomal membrane to prevent leakage of lysosomal enzymes into the cytoplasm or extracellular spaces. Such leakage has been proposed by other investigators as a critical ingredient in the aging process.

In his experimental work, the California investigator administered the *p*-chlorophenoxyacetic acid ester of DMAE to 32 male Swiss Webster Albino mice at the rate of 0.3 Gm./L. of drinking water. The mice were given routine care and fed on a standard commercial pellet diet. A control group of 31 mice was treated identically except for the inclusion of DMAE.

Mean survival time for the control mice was 9.73 months after the onset of the experiment, while the survival time of the drug-treated animals was 12.39 months, or 27.3 per cent longer than the controls, he reported recently in *Experimental Gerontology*.

In addition, there were significant differences in fluorescent pigment density; mice given DMAE showed considerably less pigmentation than did the controls. And "the brains of the control animals appeared darker in color under visual examination than did those of the drug-treated mice, whose lighter color was similar to that of young animals of the same strain examined on the same occasion. The drug-treated mice were also observed to have less mesenteric fat than did the control animals."

In an experiment with sand mice, Mr. Hochschild found that beginning drug treatment well past the mean expected life span of the animals resulted in a mean survival time of 56.9 days past the onset of the experiment for the controls and 85.1 days for the treated group, a 49.5 per cent increase over the controls.

"It can be concluded that life span may be influenced pharmacologically well into old age," he said, suggesting further that because of its very low toxicity to man, DMAE is a prime candidate for further study in relation to its action as a membrane stabilizer and its role in the human aging process.

## Piperamic Acid Active Against Infections

Medical Tribune Report

WASHINGTON—Preliminary animal studies indicate that piperamic acid, a pyridopyrimidine derivative, is orally active against *Pseudomonas aeruginosa* and has low toxicity, according to Dr. Masanao Shimizu, of the Research and Development Division, Dainippon Pharmaceutical Company, Osaka, Japan.

The agent is active against bacteria resistant to penicillin and nalidixic acid, and additionally is stable with respect to metabolic inactivation, he told the 13th Interscience Conference on Antimicrobial Agents and Chemotherapy.

Piperamic acid was more effective in combating ascending kidney infections due to *Escherichia coli* and *Klebsiella pneumoniae* in mice than either penicillin, nalidixic acid, cephalaxin, and ampicillin, Dr. Shimizu noted.

"No abnormalities were observed," Dr. Shimizu reported, after serial oral administration of the agent in mice at a dose of 4,000 mg./Kg. once daily for four weeks or in rats at a dose of 1,600 mg./Kg. once daily for two weeks.

Coinvestigators were Drs. Yoshiyuki Takase, Shinichi Nakamura, Hiromi Katase, Akira Minami, and Katsuhisa Nakata.



## C I B A



## Teeth to Be Implanted

## Public Ranks Scientists

## Public Ranks Scientists

People in the Deep South with low incomes or living in rural parts of the country have less confidence in scientists than those economically better off and those in the more developed parts of the country. "That more 'liberal' Americans might add to this main source of discontent is suggested by the fact that those who intended to vote for McGovern were less favorable to scientists than those who intended to vote for Nixon, by a margin of 33 to 41 percent." Amitai Etzioni, Ph.D., Clyde Z. Nunn, Ph.D., editorial. (*Science* 181:1123, September 21, 1973.)

## Organ Donation

"This is not just idle speculation—organ transplantation will one day become more comparable to, say, blood transfusion, and then the problem of donation from an unrelated living person will have to be faced." Carl H. Fellner, M.D., perspective. (*Ann. Intern. Med.* 79:589, October, 1973.)

Dr. C. D. Marsden, of King's College Hospital and the Institute of Psychiatry.

Drs. P. Rondet and L. J. R. Dumas, of the University of Paris, reported that more than 70 per cent of patients treated with the new medication achieved "good results"—that is, they were able to resume professional activity or an active social life.

Investigators at the University of Florida will be removing the front teeth of 24 baboons and replacing them with synthetic teeth in an experiment aimed at cutting dental costs for human beings. The synthetic teeth will be made from material that incorporates into the bone by natural growth.

# pHisoHex Guidelines

contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entrodol (sodium octylenoxyethylhexyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterol 0.2%, methylcellulose, polyethylalcohol, polyethylalcohol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.



**pHisoRx®**  
mild antibacterial soapless skin cleanser  
pHisoRx contains a colloidal dispersion of sodium lauryl sulfate 3% in a stable emulsion consisting of polyethylene glycol monophenoxethoxyethyl ether surfactant 30%, petroleum 7%, lanolin cholesterol 8%, phytosterols, ceresinone, benzoin, polyethylene glycol, polyethylene glycol, polydimethylsiloxane, benzoin, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.

Indications: pHisoRx has bacteriocidal activity against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use.

Contraindications: pHisoRx is indicated for use as a surgical scrub and a bacteriocidal cleanser.

skin cleanser. It may also be used for washing clothing after an outbreak of gram-positive infection.

Good hospital practice has been necessary as a total program of infection control. It should be used only as long as necessary for infection control.

Contraindications: pHisFax should not be used on burned or denuded skin. It should not be used as an occlusive dressing, or for debridement. It should not be used routinely for preoperative skin preparation. (a) It should not be used in total body bathing or immersion; (b) on any mucous membranes; (c) on any open wounds; (d) on persons with sensitive skin; (e) on any of its components. It should not be used on persons who have demonstrated primary hypersensitivity to halogenated phenol derivatives.

because of the possibility of cross-sensitivity to hexachlorophenol *after use*, especially from sensitive areas such as the scrotum and perineum. If left in contact with burned or denuded skin or mucous membranes, sufficed to cause toxic symptoms. Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophenol absorption. Systemic toxicity should be mentioned as a result of stimulation (irritation) of the central nervous system, sometimes with convulsions.

**PHOSPHORUS** should be discontinued promptly if signs or symptoms of cerebral irritation appear. The acute clinical and clinical evidence indicates that hexachlorophenol

## Another Growth Hormone Isolated From Human Blood

It is somatomedin, Dr. Van Wyk explained, that stimulates skeletal growth and growth throughout the body. Somatomedin, much like insulin, stimulates glucose metabolism in fat tissue and the manufacture of muscle protein. Dr. Van Wyk also said somatomedin is required for the growth of tumor cells in tissue culture.

To be called a somatomedin, Dr. Vondra Wyk summarized, a substance must be under the control of growth hormone to some extent, it must be insulinlike in its actions, and it must stimulate cell growth in one or more tissues.

## Learning to Cope



Stanford University Hospital has set up a fully furnished house on its grounds to serve as a temporary residence for patients and their families to help them learn to cope with a long-term handicap or disability.

## Internal Bleeding May Be Arrested By Modified Clot

Thrombin is usually added to the blood clot, Dr. Bookstein said;  $\epsilon$ -aminocaproic acid is sometimes added to delay lysis, and platelets are also added sometimes.

But, with the modified clots he uses, Dr. Brookstein said, "the procedure is rapid, the bleeding stops immediately and the catheter can be removed at once."

## Ultimate Feasibility Of Lung Transplants Shown in Animal Tests

"The importance of this work is that it documents the fact that lung transplantation in itself is compatible with protected good function of the transplant," said Dr. Frank J. Velth, chief of vascular surgery at Montefiore. "It means that the process of removing a lung and cutting the nerve supply and lymphatics to the lung do not necessarily produce injury or poor function in that lung. The work supports the ultimate feasibility of successful bilateral lung transplantation if the problems associated with rejection and immunosuppression can be predictably and dependably solved."

**Use**  
as a surgical scrub.

**Use**  
as a bacteriostatic skin cleanser  
against staphylococci and other gram-  
positive organisms.

**Use**  
at home as a hand cleanser for those  
who tend the bedridden patient or  
handle infants.

**Use** for washing to control outbreaks of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. Use only as long as necessary for infection control.

**Rinse thoroughly after use.**

**Do not use**

on burned or denuded skin or as an occlusive dressing, wet pack, or lotion.

**Do not use**  
as routine, prophylactic body wash.

**Do not use**  
as a vaginal pack or tampon, or  
on any mucous membranes.

toxicity is reversible.

in a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on a burned skin or exposure to a powder accidentally containing approximately 6.5% hexachlorophene. Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene.

phisoHex is intended for external use only. If swallowed, phisoHex is harmful especially to infants and children. phisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula.

or other medications.

**Precautions:** pilsollet suds that get into the eyes accidentally during washings should be rinsed out promptly and thoroughly.

**Adverse Reactions:** Dermatitis and photo-sensitivity. Sensitivity to hexachlorophenol is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophenol.

In persons with highly sensitive skin, the use of plioflex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

accidental ingestions of pHloflax in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDA for details.

How Supplied pHloflax is available in unbreakable plastic squeeze bottles of 5 ounces, 1 pint, and in plastic bottles of 1 quart.

**Winthrop Laboratories**  
New York, N.Y. 10016



A patient of mine died in his sleep on March 5, 1970, at the age of 69. I had



# ROCHE announces new

# BACTRIM<sup>TM</sup>

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

## a new type of antibacterial for a two-pronged attack against chronic urinary tract infections due to susceptible organisms

Bactrim is highly effective in the treatment of these infections — primarily pyelonephritis, pyelitis and cystitis — when due to susceptible organisms. This efficacy is related to the unique mode of action against bacteria (see illustration), an action that, in effect, makes Bactrim a new type of antibacterial.

### Bactrim interrupts the life cycle of susceptible bacteria

Unique mode of action interrupts the life cycle at two important points, thereby impeding the production of nucleic acids and proteins essential to these bacteria. These consecutive interruptions occur because sulfamethoxazole and trimethoprim resemble naturally existing substrates. By competitive replacement of these substrates, they inhibit further synthesis.

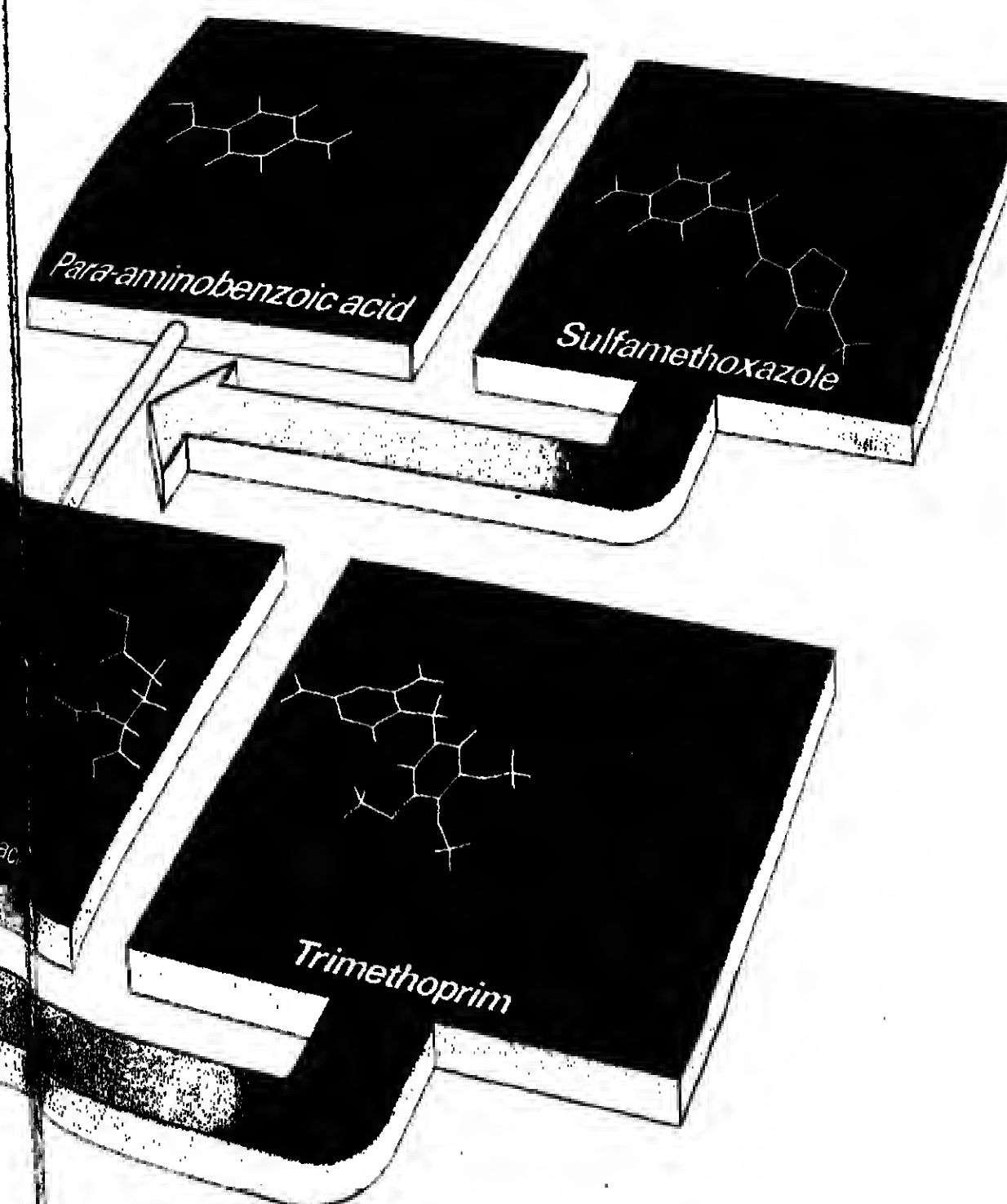
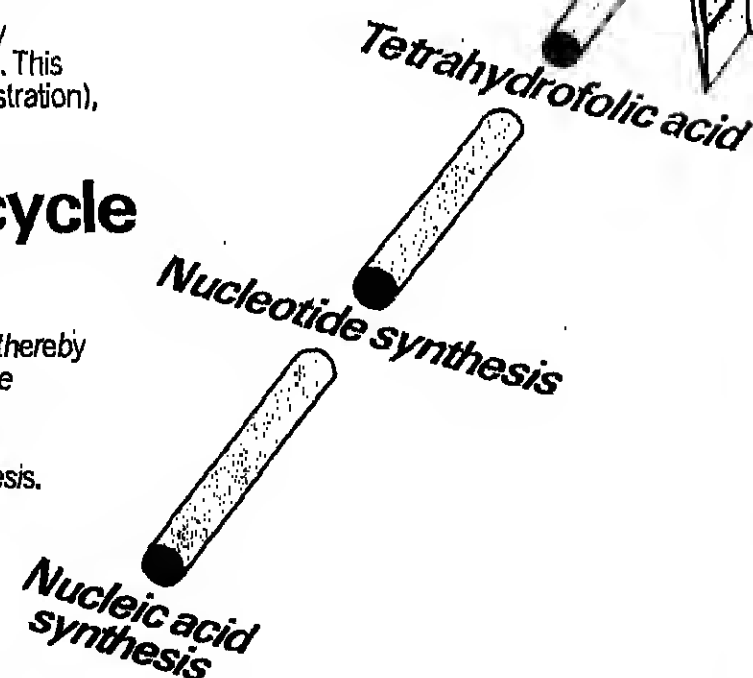
### Prescribing considerations

**Clinical Limitations:** Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of chronic and recurrent urinary tract infections. Not recommended for children under twelve.

**Contraindications:** Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period.

**Warnings and Precautions:** Both sulfamethoxazole and trimethoprim have been reported to interfere with hematopoiesis. Complete blood counts should be done frequently. If a significant reduction in the count of any formed blood element is noted, Bactrim should be discontinued. Bactrim should be given with caution to patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. Maintain adequate fluid intake. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

**Adverse Effects:** Among the most common side effects are nausea, vomiting, rash, leukopenia and elevations in SGOT and creatinine.



### Excellent clinical response in chronic urinary tract infections even with obstructive complications

A multiclinic, double-blind study\* of response to a ten-day course of therapy in 471† patients with chronic urinary tract infections demonstrated the superiority of Bactrim. On the 10th day after initiation of therapy, 91.7% (of 168 patients) showed significant

bacteriological response to Bactrim, compared with 81.2% (of 144 patients) to trimethoprim and 64.5% (of 155 patients) to sulfamethoxazole. More than half of these patients had obstructive complications.

### Excellent response maintained

Bactrim proved equally impressive in maintaining this bacteriological response. In the above study, after a ten-day course of therapy with Bactrim, 68.4% of patients with chronic urinary tract infections maintained response for up to 42 consecutive days, compared with

59.7% with trimethoprim and 44.4% with sulfamethoxazole. These results are particularly noteworthy considering the number of patients with obstructive complications — cases regarded as being notoriously difficult to treat.

\*Data on file, Hoffmann-La Roche Inc., Nutley, N.J. 07110  
†4 patients not available for evaluation at day 10.

# new BACTRIM<sup>TM</sup>

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

## for chronic urinary tract infections

Before prescribing, please see complete product information on following page.



Rx  
Bactrim  
Tablets #40  
Sig: TI B.I.D.



- ☐ New type of antibacterial
- ☐ Unique dual mode of action
- ☐ Effective against susceptible urinary tract invaders: usually *E. coli*, *Klebsiella-Enterobacter*, *P. mirabilis*, and, less frequently, indole-positive proteus species
- ☐ No loading dose
- ☐ B.I.D. dosage
- ☐ Usual therapy: 10-14 days
- ☐ Excellent response in chronic urinary tract infections, primarily pyelonephritis, pyelitis and cystitis, due to susceptible organisms
- ☐ Impressive response in cases with urinary obstruction

#### Complete Product Information:

**Description:** Bactrim is a synthetic antibacterial combination product, available in scored light-green tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole.

Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine. It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.3.

Sulfamethoxazole is N-(5-methyl-3-isoxazolyl) sulfanilamide. It is an almost white in color, odorless, tasteless compound with a molecular weight of 253.28.

**Action:** Microbiology: Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, Bactrim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

*In vitro* studies have shown that bacterial resistance develops more slowly with Bactrim than with trimethoprim or sulfamethoxazole alone.

*In vitro* serial dilution tests have shown that the spectrum of antibacterial activity of Bactrim includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa*. The following organisms are usually susceptible: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis* and indole-positive proteus species.

Representative Minimum Inhibitory Concentration Values for Bactrim-Susceptible Organisms (MIC—mcg/ml)				
Bacteria	Trimethoprim alone	Sulfamethoxazole alone	TMP/SMX (1:20) TMP	SMX
<i>Escherichia coli</i>	0.05–1.5	1.0–245	0.05–0.5	0.95–9.5
<i>Proteus spp.</i>	0.5–5.0	7.35–300	0.05–1.5	0.95–28.5
<i>Klebsiella-Enterobacter</i>	0.5–1.5	7.35–30	0.05–0.15	0.95–2.85
<i>Proteus mirabilis</i>	0.15–5.0	0.735–245	0.05–1.5	0.95–28.5

**Human Pharmacology:** Bactrim is rapidly absorbed following oral administration. The blood levels of trimethoprim and sulfamethoxazole are similar to those achieved when each component is given alone. Peak blood levels for the individual components occur one to four hours after oral administration. The half-lives of sulfamethoxazole and trimethoprim, 10 and 16 hours respectively, are relatively the same regardless of whether these compounds are administered as individual components or as Bactrim. Detectable amounts of trimethoprim and sulfamethoxazole are present in the blood 24 hours after drug administration. Free sulfamethoxazole and trimethoprim blood levels are proportionately dose-dependent. On repeated administration, the steady-state ratio of trimethoprim to sulfamethoxazole levels in the blood is about 1:20.

Sulfamethoxazole exists in the blood as free, conjugated and protein-bound forms; trimethoprim is present as free, protein-bound and metabolized forms. The free forms are considered to be the therapeutically active forms. Approximately 44 percent of trimethoprim and 70 percent of sulfamethoxazole are protein-bound in the blood. The presence of 10 mg percent sulfamethoxazole in plasma decreases the protein binding of trimethoprim to an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

**Excretion:** Bactrim is chiefly by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. When administered together as Bactrim, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

**Indications:** Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, and, less frequently, indole-positive proteus species).

**Important note:** Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of all antibacterial agents, especially in the treatment of chronic and recurrent urinary tract infections.

**Contraindications:** Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period (see Reproduction Studies).

**Warnings:** Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but it has been reported to interfere with hematopoiesis in occasional patients. In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported.

The presence of clinical signs such as sore throat,

fever, pallor, purpura or jaundice may be early indications of serious blood disorders. Complete blood counts should be done frequently in patients receiving Bactrim. If a significant reduction in the count of any formed blood element is noted, Bactrim should be discontinued.

At the present time, there is insufficient clinical information on the use of Bactrim in infants and children under 12 years of age to recommend its use.

**Precautions:** Bactrim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

**Adverse Reactions:** For completeness, all major reactions to sulfonamides and to trimethoprim are included below, even though they may not have been reported with Bactrim.

**Blood dyscrasias:** Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia.

**Allergic reactions:** Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis.

**Gastrointestinal reactions:** Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis.

**C.N.S. reactions:** Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness.

**Miscellaneous reactions:** Drug fever, chills, and toxic nephrosis with oliguria and anuria. Pericarditis nodosa and L.E. phenomenon have occurred.

Two sulfonamides bear certain chemical similarities to some gonitogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Gonit production, diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the gonitogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

**Dosage and Administration:** Not recommended for use in children under 12 years of age.

The usual adult dosage is two tablets every 12 hours for 10 to 14 days.

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	2 tablets every 24 hours
Below 15	Use not recommended

**How Supplied:** Tablets, containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose<sup>®</sup> packages of 1000; Prescription Packs of 40, available singly and in trays of 10. Imprint on tablets: ROCHE 50.

**Reproduction Studies:** In rats, doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palates. The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. However, in one study, cleft palates were observed to one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim.

In rabbits, trimethoprim administered by intubation from days 8 to 16 of pregnancy at dosages up to 500 mg/kg resulted in higher incidences of dead and resorbed fetuses, particularly at 500 mg/kg. However, there were no significant drug-related teratological effects.

new

**BACTRIM**

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

for chronic urinary tract infections

Roche Laboratories  
Division of Hoffmann-La Roche Inc.  
Nutley, N.J. 07110

Wednesday, November 14, 1973

MEDICAL TRIBUNE

19

## One Man...and Medicine

ARTHUR M. SACKLER, M.D.,  
International Publisher, Medical Tribune



### An Open Letter To Bernard Malamud On 'Rembrandt's Hat' and 'The Talking Horse'

Dear Bernie:

How the memories flood in. P.S. 181 and Rose Goldstein, Erasmus Hall and Gravesend Avenue, the little delicatessen and the "big" dreams.

What do I think of *Rembrandt's Hat*? Well, how should I put it? I didn't know which was more moving, the stories or the dedication:

To Ebba, Herb, Hans, George,  
and to the memory of Gene

\* *Rembrandt's Hat* by Bernard Malamud  
Farrar, Straus and Giroux  
19 Union Square West  
New York, N.Y. 10003.

That's as great praise as I can give. Of course, only you and Ebba, Herb, Hans, George, and maybe two or three others in the world would understand.

This isn't a book review. Hell, I couldn't write one to save my life. I write of *Rembrandt's Hat* and its eight short stories as a "life review." For me, each of the eight stories wove strand after strand into a pattern of life—from "The Silver Crown" to "The Talking Horse"; each added to it color as well as design.

"The Silver Crown" encapsulated so much of what has happened—an much that you didn't know about. It was not just Gans, the father, dying in the hospital of cancer, and Albert Gans, the biology teacher, ambivalently abandoning his intellectual convictions to fulfill his emotional needs. It is everybody's struggle between perceived reality and the unconscious drives of mystic faith or wishful hope when reality becomes painful.

For me, so much of science has been so much of faith. But what does one do when science fails? Most fall back on "faith." We reject the inevitability of death. Who among us can accept the mortality of a loved one? But reality always, as it always must, ensues illusion.

You probably didn't know Sophie smoked. When the thoracic surgeon saw her chest plot, he said, "Look, fellows, you're all doctors; I'll give it to you straight. I know you don't smoke; otherwise I'd say mom has a bronchogenic ca." Forty-eight hours later he did a pneumonectomy. Ca. But who gives up? We checked all the top experts. Nothing. The world literature. Nothing. Agall and again—nothing. We hear of a rabbi who's a brilliant biochemist who believes he has a new anticarcinogen—on antibiotic. He asks no silver for the Silver Crown. An honest guy, compassionate, warm. We inject the new antibiotic—crude and, later, more refined batches. We try everything. We "fight" until she says, "Does it have to be so hard to die?" For us there was good faith and wishful hope, for too many bad faith—but regardless of faith or hope or not, all our loved ones, as we, too, will "shut our eyes."

#### Are We Followed?

To "Man in the Drawer," your American tourist, the writer Howard Harvitz, got to Kiev, Leningrad, and Moscow. On our trip to the U.S.S.R. we made Leningrad and Moscow but not Kiev. We had the same feeling, always the feeling, are we followed? We met brilliant doctors and scientists, statisticians, and humanists. Most of those we met spoke excellent English, colloquial American, not like your writer Levitsky. Harvitz, the American author, really had it tough. His wrestling with himself was tougher than with his Russian fellow writer Levitsky. Harvitz was a battleground on which fear and principle struggled in the battle between Harvitz' safety and the rights and the desperate plight of his half-Jew fellow writer and fellow man.

Truth can be as strange as fiction. In Leningrad, while we were being escorted

through the Hermitage, we noted that a strange, well-dressed young man had "attended" himself to one of our daughters. He claimed to be a Rumanian student on vacation and was carrying superb, complex cinematic equipment. When we got back to the Astoria (where your Harvitz stayed), the girls told us that the young man had given them a letter to post when we left the country, a letter to "a friend in New York." It was quickly "shredded" and down the toilet bowl. Harvitz had a conflict. We had none; we were on an official mission, and our young ones had to learn the rules. They had almost placed our mission in jeopardy. Later, on several occasions, we were to ask each other—is this guy or that guy NKVD or CIA?

Fine plays funny tricks. You were always going to be a writer, I a doctor. Writing was brenth to you; psychiatric research was medicine for me. I watch your climb toward the peak of your Olympus. I go from psychiatry into biology, and you as a writer practice psychiatry.

#### "The Letter" Rocked Me

Your next story, "The Letter," really rocked me, Bernie. Was your Teddy one of my old patients? If my contact with reality were less secure, I'd say we were together when I worked at Creedmoor State Hospital. Eight pages of sheer, clinical facts; the reality of those who suffer "delusions"—or are they really delusional? And in "My Son the Murderer," again the gap between the different realities—in that case of the generations and the social dislocation so common to postadolescence.

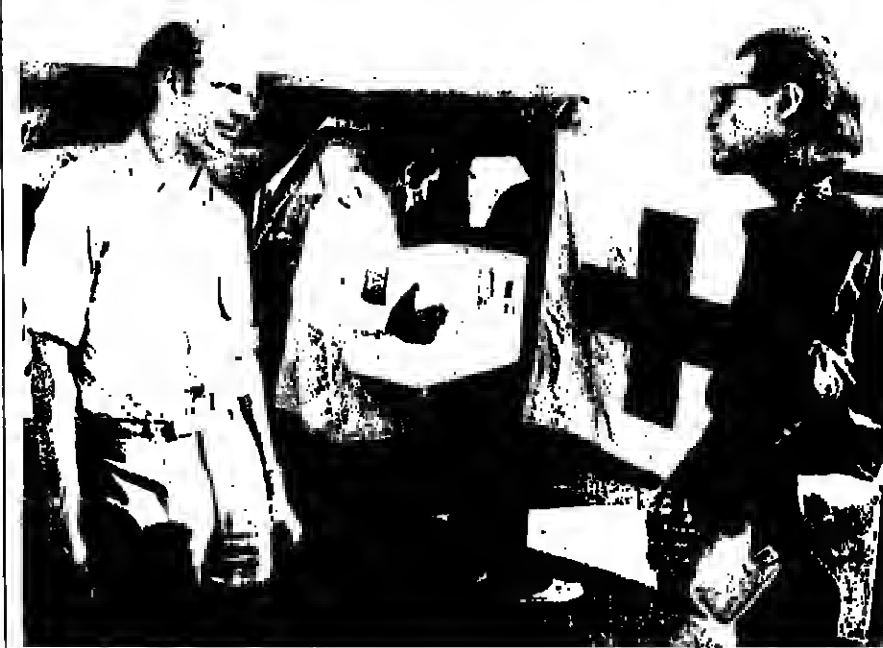
In "Retirement" you immerse us into the geriatric disease of loneliness—the rejection of age, the clinging to youth, and, once again, the illusion, the hope, the faith which is "respectfully yours, Simon Morris, M.D."

Then, in "Rembrandt's Hat," as Rubin, the artist, struggles with Arkin, the "hypertensive, impulsive" art historian, we witness a wordless battle, a classic of one aspect of modern psychology and psychotherapy—nonverbal communication. But whether it was Rembrandt's or someone else's hat, will man always have to wear the crown of failure and hope?

What should I say of "Notes From a Lady at a Dionce Party"? If life plays tricks on the old ones and youth tantalizes others and herself, one has to adapt from what one learns from practice to life—let's have patience with our patients. I say "our patients." The clinical acuity, the insights into the conflicts of the emotional games people play, and the visual clarity of your characters' physical status all make for classic case histories. These stories are musts for medical students, who must learn to observe the telltale signs and symptoms so critical to diagnosis and medical prognosis.

What story did I like best? "Talking Horse," of course. How could one born and bred in Brooklyn fail to identify with a talking horse with such a genuine Brooklyn "accent"? Nay,

### Blood for Trapped Egyptian Troops



An International Red Cross official (left) accepted blood plasma from Israeli Army officers for a special airlift to the Egyptian III Corps trapped on the eastern bank of the Suez Canal before Egypt was allowed to send in food and medicine under United Nations supervision.

How can one fail to love your Abramowitz, the talking horse, more than human in his feelings and frustrations? Is he Abramowitz, a horse, or a horse including Abramowitz? Locked in an indissoluble partnership with his deaf-mute owner and master, Abramowitz, the talking horse, can only have his "theories, guesses, but can't prove a thing." How many of us can? His master, Goldberg, doesn't seem interested in woe-meo "but sees to it that Abramowitz gets his chance at a mare in heat, if available. Abramowitz engages to satisfy his physical nature, a fact is a fact, otherwise it's no big deal; the mare has no interest in a talking cornish. Furthermore, Goldberg applauds when Abramowitz mounts her, which is humiliating."

True, Bernie, in our "circus" many seek escape in alcohol or in silence; like Abramowitz' master, they are rendered deaf and mute and unfeeling by life. A few are like the talking horse Abramowitz, and try to articulate their yearning

for freedom in action. Most, unlike the talking horse, are passive "cesseroles" incubating a goulash of dreams, hopes, and frustrations—cesseroles in "human" shapes. Since, unlike the talking horse, most are unwilling to act, most are not fated for freedom. But perhaps you're right, Bernie—what can one expect? In youth, and less often later, those who were talking horses try and try again. But who listens?

Gene would have enjoyed every page. I know Ebba and the others did, and I loved it.

Arthur



The halls of fame are open wide  
And they're always full;  
Some go in by the door called "push,"  
And some by the door called "pull."  
Anon.

## Salk Team Prepares to Test Monthly Antifertility Drug

Medical Tribune Report

SAN DIEGO, CALIF.—Scientists from the Salk Institute and the University of California here are preparing for clinical trials of a once-a-month antifertility drug.

The trials, scheduled for "sometime within the next five months," will test agents that block the production of specific reproduction hormones, said Dr. Roger Guillemin of the institute. Clinical tests will be conducted by Dr. Samuel Yen, of U.C.S.D. Medical School's Department of Obstetrics and Gynecology, under contract to Salk.

In animal studies, the antifertility agents antagonize the normal action of luteinizing hormone-releasing factors (LRF), which triggers the release of luteinizing hormone (LH) by the pituitary gland.

The testing program will be conducted under contract for the Agency for International Development.

The Salk investigators believe that it should be possible to administer the LRF antagonists effectively within the first 10 days of the menstrual cycle.

Dr. Guillemin and his group first determined that man-made analogues of LRF would inhibit secretion of LH in cultures of rat pituitary cells about 18 months ago. Since then, they have observed the same phenomenon in laboratory rats.

The materials of interest are peptides, consisting of a chain of nine amino acids, in a structure of LRF that was first proposed by a group of investigators at the VA Hospital in New Orleans.

"LRF antagonists prepared so far at

Salk Institute are probably not yet potent enough to be considered the ultimate choice," said Dr. Guillemin. "However, the antagonists we are making now are more potent than those we made six months ago, and the antagonists we made six months ago were more potent than those we made a year ago."

On the basis of extensive physical and biochemical studies, it is now well recognized that peptides such as LRF are very specific in their action, especially when compared with the "ubiquitously acting" steroids now used as contraceptives, Dr. Guillemin said, noting that their "ubiquitous nature" is the source of their frequently observed side effects.

Speaking of their possible use as antifertility agents in men, Dr. Guillemin said:

"The same type of molecule would also affect testicular function, but this aspect of their possible use is much less firmly established on experimental grounds. In fact, physiologic studies of the male reproductive system are much less well understood than those of the female."

While the antagonists look promising as antifertility agents, the group at Salk is equally interested in developing compounds that would trigger ovulation "in what would be, in the framework of fertility control, an improved rhythm method."

In addition to Dr. Guillemin, members of the Salk Institute group include Max Amos, Richard Blackwell, Roger Burgess, Geoffrey Grant, Michael Monahan, Jean Rivier, and Wylie Vale.



## Atherosclerosis May Be Evolutionary Lapse

Continued from page 1

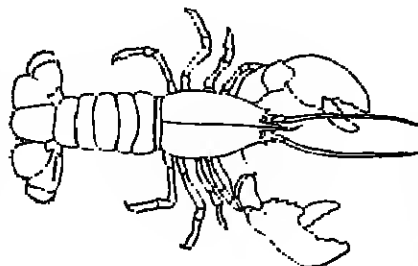
"I view the sclerotic process as a result of a mutation of some tissue elements of the arterial wall whereby it reverts to a more ancient form and produces increased amounts of transglutaminase."

Dr. Laki explains that in studies of the action of the enzyme thrombin on fibrinogen he has discovered that the resulting clot is not the type of clot formed in normal blood; the thrombin-formed clot is soluble in concentrated urea solution, while the normal blood clot is not.

"We now know that, in addition to thrombin, there is a second enzyme involved in the formation of the normal clot."

"In the clot formed by thrombin, the fibrin molecules are connected by weak hydrogen bonds. Gently warming is enough to disperse the clot. In the normal clot the second enzyme is also acting, and the fibrin molecules become connected by firm chemical bonds. Such a clot can be dissolved only by digesting it with a powerful proteolytic enzyme like pepsin."

Dr. Laki concludes that the enzyme that produces the clot needed for hemo-



stasis and wound healing is this second enzyme, which is a transglutaminase. The clot formed by thrombin is seen as a preliminary step. Transglutaminase occurs in the blood of men and other vertebrates as a precursor, Dr. Laki says.

### Has No Thrombin System

Getting back to the lobster, he explains that this animal has no thrombin system. In the lobster, fibrinogen is clotted directly by a powerful transglutaminase released from tissues.

Human fibrinogen also can be clotted directly by high concentrations of transglutaminase.

"In other words, increased amounts of

this enzyme can be as dangerous as its absence," he says, adding that transglutaminase "can clot fibrinogen directly even if the thrombin system is switched off with coumarin or inhibited with heparin."

If such direct clotting occurs, "the patient may die from thrombus formation (fibrinogen clot) in spite of the presence of coumarin or heparin medication."

"I believe most physicians do not realize the possibility of this danger."

Dr. Laki put rabbits on a high cholesterol diet for several weeks and then, after sacrifice, studied portions of aorta that were heavily affected with sclerotic plaques. These portions contained an average of three times as much transglutaminase as healthy specimens of aorta.

The actual plaques comprised no more than 10 per cent of the diseased portion of the tissue, which means that some tissue elements of the arterial wall had high levels of transglutaminase.

Dr. Laki says he believes that it is in the smooth-muscle layer of the arterial wall that a mutation of some tissue elements causes the arterial wall to revert to a more ancient form—that of the lobster—and produce increased amounts of

transglutaminase, with resulting atherosclerosis.

"The reason for my belief is that a tissue element otherwise low in transglutaminase content is the most likely one to have mutated to be a rich source of transglutaminase, and muscle tissue, in general, is low in transglutaminase."

### Result of Genetic Mutation

"In this view, atherosclerosis is the result of a genetic mutation, either brought about spontaneously or by some outside effects—like feeding a high-cholesterol diet to rabbits."

Dr. Laki suggests that freshly formed clots blocking diseased vessels be tested to see if the addition of thrombin to the homogenized thrombus releases fibrinopeptides and if the dipeptide, γ-glutamyl-lysine, can be isolated.

If such a study were to confirm his proposals, Dr. Laki believes, the next step would be to find specific inhibitors of the transglutaminase system.

## Is NIH's Control Over Research Being Removed?

Continued from page 1

University of Michigan at Ann Arbor; Philip Handler, Ph.D., president of the N.A.S.; Dr. Robert Q. Marston, former head of the National Institutes of Health, fired by the Nixon Administration; and Dr. Jesse Steinfeld, former U.S. Surgeon General; and Dr. Robert W. Berliner, former scientific director of the NIH, now dean of the Yale University School of Medicine.

MEDICAL TRIBUNE is withholding identification of the other participants, some of whom are "household" names in the medical and biomedical research communities.

Former HEW Secretary Cohen told MEDICAL TRIBUNE of "the shattering impact" of the Administration's attempt to gain control of the research structure at the National Institutes of Health.

He charged that the White House "now calls the signals in biomedical research."

### May Harm Research Setup

Some of those at the meeting expressed fears that the Administration—via the White House's Office of Management and Budget and the Secretary of Health, Education, and Welfare, Caspar Weinberger—is doing serious harm to the country's research structure.

A top HEW official, however, described the White House's position as a belief that "research is an open hole; it can absorb all the money you can throw into it. We've got to get some control over it. There is a limit to how much we are willing to spend."

The alleged policy of research structure containment, Mr. Cohen stated, has caused "a state of anxiety, frustration, and concern at NIH," a feeling that there is not enough reliance on the scientific and professional skills of NIH's researchers, with outside forces now making research policy.

"Fundamentally, this is a very upsetting thing," Mr. Cohen added, warning that the administration's new approach "is very unwise."

The abolition of the NIH's scientific advisory committees, the leveling off of basic research funds in favor of expanding cancer research and contract research, the firing of NIH officials, and the Bureau of the Budget's review of research policies—"coming all at the same time"—have spread alarm and dismay in the research community, he said. "There has never been a situation like this before. Do these political people understand biomedical research? Don't they realize that contract research won't get the job done quicker?" Mr. Cohen asked.

He contended that "you've got to give [the NIH research structure] a lot of leeway" and questioned the Administration's entire attitude toward research.

## Dali Winners, 5th List

- ANDREWS, JAMES C., M.D., 801 East High Street, Charlottesville, Va.
- APPLE, GEORGE W., JR., M.D., Box 158, Plano, Tex.
- AUSBON, W. W., M.D., 447 5th Avenue South, Naples, Fla.
- BENZ, CHARLES C., M.D., 1322 N. Vermont Avenue, Los Angeles, Calif.
- BERLANGA, RAFAEL, M.D., 111 7th Street, Garden City, N.Y.
- BLAKEY, LESLIE W., M.D., 1221 S. Broadway, Lexington, Ky.
- BOESKY, DALE, M.D., P.C., 2401 W. Big Beaver Road, Troy, Mich.
- BRENDZE, ROBERT H., M.D., Zero Emerson Place, Boston, Mass.
- BROWNINO, C. M., D.O., 225 S. Main, Memphis, Mo.
- BRYANT, FRANK L., M.D., 4421 Creswell, Shreveport, La.
- CAMARDA, ANTHONY L., M.D., 690 Clinton Avenue, Bridgeport, Conn.
- CHANDLER, WILLIAM M., M.D., 6728 Point Drive, Edina, Minn.
- CHRISTIAN, JOHN D., M.D., 5520 W. Markham, Little Rock, Ark.
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- COZEN, HAROLD, M.D., 2326 Redondo Beach Boulevard, Gardena, Calif.
- CROWELL, THEODORE, M.D., 2223 E. Day Island Blvd., Tacoma, Wash.
- DAVIS, PAUL H., M.D., 636 Beacon Street, Boston, Mass.
- DEAN, GILBERT O., M.D., 220 Ridgeway, Little Rock, Ark.
- DEMAREST, AUDREY P., M.D., 110 Clarke Street, Syracuse, N.Y.
- DERMOTT, ROBERT V., M.D., 141 Camino Alto, Mill Valley, Calif.
- DONOVAN, JAMES M., M.D., 1325 S. 72 St., Omaha, Neb.
- DUNCAN, FURM M., JR., M.D., 2318 E. Kessler, Longview, Wash.
- EDELSTEIN, JOSEPH B., M.D., 358 Park Avenue West, Mansfield, Ohio
- ENGLISH, R. E., D.O., 5509 Central Avenue, N.W., Albuquerque, N. Mex.
- FOSTER, JULIAN L., M.D., 3500 South University, Little Rock, Ark.
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- GANO, LAWRENCE B., M.D., 1016 6 Avenue, Huntington, W. Va.
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- GEORGE, RICHARD L., M.D., 902 Second Avenue North, Columbus, Miss.
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- GOLPER, MARVIN N., M.D., 411 Morningside Drive, Kokomo, Ind.
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- GRAD, ED., JR., M.D., 5541 Fox Road, Cincinnati, Ohio
- GRANDT, EDWARD J., M.D., 600 Ivy Street, Elmhurst, N.Y.
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- HESTER, JOE, M.D., 419 Cunningham Drive, Muskogee, Okla.
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## 'Keiro' Means Home for Elderly



The word "keiro" means "nursing home for the respected elders," masking it an appropriate name for a nursing facility in Los Angeles that was constructed with funds donated by the Japanese-American community and molded to Oriental tastes.

## Anterior Urethral Valve Seen In Some Obstruction Cases

Medical Tribune Report

CHICAGO—Boys with signs and symptoms of urethral urinary obstruction should be carefully evaluated for anterior urethral valves, the American Academy of Pediatrics was told here. The diagnostic work-up should include voiding films during cystourethrography, careful urethroscopy, and examination of the anterior urethra—particularly when there are obstructive symptoms.

Although posterior urethral valves have been recognized as a relatively common cause of severe bladder outlet obstruction, anterior urethral valves have received much less attention "and even today are not always included in the differential diagnosis of boys with symptoms suggesting bladder outlet obstruction," stated Drs. Csirmir F. Firlit and Lowell R. King, of the Department of Urology, Northwestern University, and the Division of Urology, the Children's Memorial Hospital, here.

## Did You Say Dali? Here's a Story To Go With Print

Medical Tribune Report

Last week the genius and unpredictable character of Dali as revealed to his autobiography, *The Secret Life of Salvador Dali*, was discussed by Dr. Arthur M. Sackler, international publisher of MEDICAL TRIBUNE, in his column. Another revealing story comes from John Oruen, whose book *The Party's Over* is an art history of the 1950s. Mr. Oruen was working as a clerk in Brentano's bookstore when, as he describes it, "Dali walked up to me and asked if I had a copy of his *Secret Life of Salvador Dali*. I quickly fetched the book and said, 'Here you are, Mr. Dali.'"

"He asked whether I had read it, and I had to admit that I hadn't. He then said that he would take the book, and would I gift-wrap it. I did so with alacrity and banded him the package."

"He now banded the book back to me saying, 'Take it. It is my gift to you. Would you like me to autograph it for you?' I tore open the gift wrapping, found him a pen, and, in the largest possible letters, he scrawled his name—and mine—upon the frontpiece. Mr. Dali omitted one vital step in the transaction. He walked out of the shop without paying for the book. Needless to say, the book still rests upon my bookshelf—Brentano's gift to me."

The Chicago urologists warned that the anterior urethral valve may easily be overlooked at initial evaluation. To avoid missing the defect, a lateral or oblique view of the entire urethra must be obtained during voiding cystourethrography. "Similarly, the anterior urethra must be carefully examined at the time of cystoscopy."

Although review of the literature revealed only 14 reported cases, an additional seven boys were found among the 74 urethral valve patients diagnosed and treated at Children's Memorial Hospital from 1952 to 1971. The remaining 67 had posterior urethral valves.

Most patients presented for urologic evaluation because of impeded urinary flow, although one was brought for examination because of urinary tract infection. Ages of the patients ranged from two days to 11 years. "Two patients less than one week of age who were found to have anterior urethral valves have been seen within the last 18 months."

Of the seven boys with anterior urethral valves, two presented with large urethral diverticula, which, of course, suggested the proper diagnosis. Drs. Firlit and King cautioned that "several of the patients underwent repeated hospitalizations because of symptoms suggesting intravesical obstruction before the proper diagnosis was made."

Early diagnosis, they continued, should minimize the morbidity associated with unnecessary or inappropriate surgery and reduce the incidence of urinary tract infection.

Specifically, they recommend transurethral resection and/or fulguration for anterior urethral valve. When the condition is associated with a diverticulum, they perform open resection of the valve together with excision of the diverticulum, with suprapubic cystostomy for temporary diversion.

## PAHO Reports Smallpox Eradicated in Americas

WASHINGTON—The Pan American Health Organization reports that smallpox has been eradicated from the Americas. The last case of the disease was reported on April 19, 1971, in Brazil.

Efforts to eradicate smallpox in the Americas started in May, 1949, when member governments adopted a resolution urging massive vaccination.

Between 1948 and 1971, in American countries in which the disease was endemic, 208,575 cases are known to have occurred.

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## When G.I. complaints occur in the absence of organic findings, underlying anxiety may be one factor

### The influence of anxiety on gastrointestinal function

Excessive anxiety and tension can adversely affect the function of any portion of the gastrointestinal system. Complaints are varied, e.g., epigastric pressure, heartburn, ulcer-like pain, diarrhea, etc. A vicious circle may develop in which anxiety and G.I. disorders intensify each other.

Prime objectives of total patient therapy include: symptomatic relief, removal of apprehensions about organic disease and helping the patient understand how excessive anxiety may trigger physical complaints. Brief counseling and the utilization of favorable factors in the patient's personality and environment can often provide needed support.

### Antianxiety therapy

Antianxiety medication may prove a valuable supplement when counseling and reassurance are not sufficient to allay the patient's emotional distress and relieve his anxiety-provoked physical complaints. The agent prescribed should be both clini-

cally effective and generally free from undesirable side effects. Librium meets these requirements with a high degree of consistency, and has a wide margin of safety and an excellent record of patient acceptance. The most common side effects reported have been drowsiness, ataxia and confusion, particularly in the elderly and debilitated.

Whenever anxiety is a clinically significant factor, adjunctive Librium is used concomitantly with specific gastrointestinal drugs, such as anticholinergic agents. Once anxiety has been reduced to appropriate levels, treatment with Librium should be discontinued.

### For relief of excessive anxiety

adjunctive

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Before prescribing, please consult complete product information, a summary of which follows:

**Indications:** Relief of anxiety and tension occurring alone or accompanying various disease states.

**Contraindications:** Patients with known hypersensitivity to the drug.  
**Warnings:** Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

**Precautions:** In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in

presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

**Adverse Reactions:** Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction, changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

**Supplied:** Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Librilabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.



## Dialysis Payment Fight Unites Nephrologists

Medical Tribune Report

WASHINGTON—Nephrologists across the country are uniting to fight the Department of Health, Education, and Welfare and the Social Security Administration on what the physicians regard as misadministration of the new Federal program intended to pay for 80 per cent of the costs of kidney transplantation and dialysis.

The SSA is currently some \$60,000,000 in arrears in payments to hospitals and dialysis centers, and HEW has refused to allow separate fee-for-service payments to private nephrologists who are providing "normal" treatment for stable dialysis patients.

HEW's claim is that stable patients do not require regular supervisory care of nephrologists, that any costs for such care are part of the dialysis unit's administrative overhead and are included in the lump-sum payment the SSA makes to dialysis providers, and that nephrologists should therefore arrange with the centers for any remuneration.

Dr. Eli A. Friedman, chief of dialysis at Downstate Medical Center, Brooklyn, called the Government's new rules "a national scandal." A similar fee problem

exists for private nephrologists who provide consultation and treatment services for kidney transplant patients.

The SSA has also ordered a freeze on the certification of new dialysis centers as of the date the dialysis funding law took effect—July 1.

According to Irwin Wolkstein, deputy director for policy of the SSA's Bureau of Health Insurance, to allow new certifications at this time "would be an invitation for entrepreneurs to open additional facilities . . . and when you have too many centers you increase the cost of the care and lower the quality."

The freeze has stalled a proposed unit in Brooklyn intended to be the referral center for six hospitals.

"We are holding patients suboptimally because the Brooklyn Kidney Center is unable to open," Dr. Friedman said, "and I have no other place to refer them. Some of these patients may die while waiting for the center to open."

The SSA told MEDICAL TRIBUNE that a decision on allowing some limited new certifications—"exceptions"—is due soon.

One of the nephrologists' complaints is that although the new funding legislation was enacted last year, the SSA issued

interim guidelines only one business day before it went into effect.

In New Jersey, a group of nephrologists have banded together to file suit in U.S. District Court charging the SSA with illegally promulgating the interim rules without required hearings and notice. The group hopes to secure a restraining order against restrictions in the regulations.

### SSA Says It Will Catch Up

The SSA admits the situation is confused but claims it will catch up with bills from dialysis centers by early next year. It has emergency provisions, it says, for immediate payment to any certified centers that are in dire financial straits as a result of the payment lag.

In many areas, nephrologists who have not contracted with dialysis centers for remuneration are not being paid.

Dr. Robert S. Rigolosi, director of nephrology at Holy Name Hospital in Teaneck, N.J., reported that the SSA's guidelines and failure to pay what it owed "immediately created difficulty for all existing dialysis centers and threaten every dialysis unit in the country."

Dr. Rigolosi said that HEW's view that

stable dialysis patients require no care by nephrologists is unrealistic.

At Holy Name Hospital "there are nephrologists treating dialysis patients who are working without pay, but we have made a pledge that we will treat these patients regardless" of the HEW rules, Dr. Rigolosi stated.

Dr. Robert G. Muth, director of nephrology at Research Hospital and Medical Center, Kansas City, Mo., reported that nephrologists there are also working without pay but said he is submitting documentation that nephrologists' services are required and is billing the Government for these services. He is uncertain whether the SSA will allow the claims.

Dr. Arthur I. Katz, head of the nephrology section at University of Chicago Hospital and Clinics, said he "fully disagreed" with the HEW refusal to cover fee-for-service charges by nephrologists.

Dr. Morrell M. Avram, director of the nephrology division of Long Island College Hospital and director of the new Brooklyn Kidney Center, complained that "the dialysis patient does not have a physician any more, and these are the physicians who treat the sickest of patients."

Downstate's Dr. Friedman charged that HEW, by declaring the services of nephrologists to stable patients are a part of the over-all administrative costs of the operation of dialysis centers, "in one fell swoop, socialized medicine for nephrologists."

"What this has done is to force the nephrologist to become a salaried employee of the hospital," he said.

"HEW does not understand the urgency of this situation," Holy Name's Dr. Rigolosi commented.

The SSA has set an all-inclusive limit of \$150 per dialysis on its payments for stable patients, although, according to an HEW spokesman, "we will pay more than \$150 when good reasons can be shown" for a higher charge.

Dialysis charges are said to vary around the country from a low of \$120 by some centers in New York City to some \$250 per dialysis in Los Angeles, Dr. Friedman noted.

But Dr. E. I. Becker, of New York Hospital-Cornell Medical Center, president of the National Kidney Foundation, was more sympathetic to the SSA and its regulations.

"The problems here are of such magnitude," he said, "that it will take time for them to be worked out."

The SSA's Mr. Wolkstein admitted that the agency is "not up to date with our billings." He said that it will take some months for the system to get into reasonably good order.

## Hormone Test Helps In Choosing Therapy For Tumor of Breast

Continued from page 1

ent with prolactin and estrogen or prolactin and testosterone, it would seem wise to combine both antiprolactin and anti-sex hormone measures. In this way it is hoped that such methodology may replace the surgical lottery that at present faces the individual patient with recurrent breast cancer.

Regressions of three to 18 months have been observed in hormone-dependent breast cancers following therapy suggested by the diagnostic technique developed by his tumor biology group, Dr. Hobbs said.

"As such, the in vitro test can spare a breast cancer patient with a hormone-dependent tumor an unnecessary operation. Although we cannot speak of a cure of breast cancer in any sense at this time, we believe that the test offers the patient a somewhat more comfortable life while under treatment."

In recognition of the value of the test, Dr. Hobbs and his group were recently awarded the prestigious Paul Martin International Prize. His colleagues include Drs. Herschel Flax, Hussain Saik, William Brander, and Kenneth Newton.

## situation:

Elderly... doesn't get out much anymore... whole world slowed down.

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## laxation:

Gentle, predictable and easy-to-take SENOKOT Tablets or Granules. Taken at bedtime, they usually induce comfortable evacuation in the morning. Leave your older patient feeling more like getting up and around.

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**TABLETS**

**INDICATION**  
Minimal Brain Dysfunction in Children—as adjunctive therapy to other remedial measures (psychological, educational, social).

**Specific Diagnostic Considerations**  
Specific etiology of Minimal Brain Dysfunction (MBD) is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources.

**Characteristics commonly reported include:** chronic history of short attention span, distractibility, emotional lability, impulsivity, and moderate to severe hyperactivity; minor neurological signs and abnormal EEG, is arising may or may not be impaired. The diagnosis of MBD must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics.

**Drug treatment is not indicated for all children with MBD. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders, including psychosis. Appropriate educational placement in a special and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.**

**CONTRAINDICATIONS**  
Marked anxiety, tension, and agitation, since Ritalin may aggravate these symptoms. Also contraindicated in patients known to be hypersensitive to the drug and in patients with glaucoma.

**WARNINGS**  
Ritalin should not be used in children under six years, since safety and efficacy in this age group have not been established.

Sufficient data on safety and efficacy of long-term use of Ritalin in children with minimal brain dysfunction are not yet available. Although a causal relationship has not been established, suppression of growth (ie, weight gain and/or height) has been reported with long-term use of stimulants in children. Therefore, children requiring long-term therapy should be carefully monitored.

Ritalin should not be used for severe depression of either exogenous or endogenous origin or for the prevention of normal fatigue states.

Ritalin may lower the convulsive threshold in patients with or without prior seizures with or without prior EEG abnormalities, even in absence of seizures. Safe concomitant use of anticonvulsants and Ritalin has not been established. If seizures occur, Ritalin should be discontinued.

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in all patients taking Ritalin, especially those with hypertension.

**Drug Interactions**  
Ritalin may decrease the hypotensive effect of guanethidine. Use cautiously withpressor agents and MAO inhibitors. Ritalin may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (phenobarbital, diphenhydramine, primidone), charybutazone, and tricyclic antidepressants (Imipramine, desipramine). Downward dosage adjustments of these drugs may be required when given concomitantly with Ritalin.

**Usage in Pregnancy**  
Adequate animal reproduction studies to establish safe use of Ritalin during pregnancy have not been conducted. Therefore, until more information is available, Ritalin should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks.

**Drug Dependence**  
Ritalin should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism, because such patients may increase dosage on their own initiative. Chronically abusive use can lead to marked tolerance and physical dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal, since severe depression as well as the effects of chronic overactivity can be unmasked. Long-term follow-up may be required because of the patient's basic personality disturbances.

**PRECAUTIONS**  
Patients with an element of agitation may react adversely, discontinue therapy if necessary. Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

**ADVERSE REACTIONS**  
Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include: hypersensitivity (including skin rash, urticaria, fever, anaphylaxis, eczematous dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyslexia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmias; abdominal pain; weight loss during prolonged therapy. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: leukopenia and/or anemia; a few instances of scalp hair loss.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

**DOSEAGE AND ADMINISTRATION**  
Children with Minimal Brain Dysfunction (6 years and over)

Start with small doses (eg, 5 mg before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dosage above 60 mg is not recommended. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage, or, if necessary, discontinue the drug.

Ritalin should be periodically discontinued to assess the child's condition. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Drug treatment should not and need not be indefinite and usually may be discontinued after puberty.

**HOW SUPPLIED**  
Tablets, 20 mg (pale green, scored); bottles of 100 and 1000. Tablets, 10 mg (pale green, scored); bottles of 100, 500, 1000 and 2000. Tablets, 5 mg (pale yellow); bottles of 100, 500, and 1000. Consult complete product literature before prescribing.

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**C I B A**



## Managing Wednesday's Child... the child with MBD

"Wednesday's child is full of woe" It need not be this way for the MBD child.

He can learn and adjust if given a helping hand.

Without help, the MBD child may be a slow reader, can find writing difficult, and arithmetic hard to grasp. He may be excitable, and his actions can be disruptive. The result can seriously hamper his educational and social development.

But, properly diagnosed and treated, MBD—Minimal Brain Dysfunction—can be brought under control so that the afflicted child can develop normally.

And Ritalin can play an important part in the total rehabilitation program of the MBD child, which includes remedial measures at home and at school. It's currently the drug of choice in many MBD situations.

Ritalin is well tolerated. It can help control the excessive motor activity of the MBD child and ameliorate behavioral and learning problems.

Of course, Ritalin is not indicated for childhood personality and behavioral disorders not associated with MBD.

**Ritalin®**  
(methylphenidate)  
only when medication  
is indicated



## Clinical Trials



by Olden

## New Bone Scan More Sensitive Than X-Ray

Medical Tribune World Service

MONTREAL—Bone scanning with technetium-99m-labeled diphosphonate is substantially more sensitive than x-ray in detecting metastatic disease, Dr. John D. Osmond III of the Massachusetts General Hospital reported to the American Roentgen Ray Society meeting here.

Dr. Osmond's conclusion was drawn from the first 800 scans done at Massachusetts General with this new organic bone-scanning agent, developed at the hospital early in 1971 by Castronovo and Callahan. Technetium-99m scans were compared with conventional roentgenographic studies of osseous metastases in 259 patients with histologically proven breast, prostate, and lung carcinomas.

Both bone surveys were conducted within a two-week interval; scans and standard x-rays were interpreted by two separate teams, each with two different radiologists. Although the scanner is a more sensitive detector of lesions, able to find some metastases missed by x-ray, x-ray was needed to interpret 10 per cent of the scans in this series.

## Immune Response To Cancer Indicated By Lymphocyte Test

Medical Tribune Report

CHICAGO—An in vitro test of a patient's ability to mount an immunologic response against cancer has been developed by a group at U.C.L.A.

Dr. Theodore X. O'Connell told the American College of Surgeons here that the test can be performed immediately, with no need to sensitize the patient first, permitting therapy to start sooner. Serial studies may be performed to determine changes in the immune response as a result of therapy or course of disease.

Dr. O'Connell and his investigative team found that lymphocytes from cancer patients exhibit a depressed response in blastogenic lymphocyte-function tests. "The deficit is not related to the stage of disease. Many patients with rather localized disease are markedly immune deficient. We would expect that they would have a difficult time containing their tumor and should have a rapid spread of their disease."

## Heart Muscle Can Be Saved If Revascularized Quickly

University of Hawaii Investigators

► If the heart muscle damaged by coronary occlusion can be revascularized within four hours, some of the muscle area can be preserved, said Dr. John R. Spector, University of Hawaii School of Medicine, Honolulu.

Dr. Spector and his collaborators studied the progression of the size of infarct in monkeys following acute obstruction of a major coronary artery and the effect of restoration of blood flow on the size of the infarct. Tissue studied indicated that revascularization up to four hours after the occlusion decreased infarct area.

scans and positive x-rays some metastases demonstrated by scan were missed by x-ray. Nineteen per cent demonstrated positive scans and negative x-rays. Although 2 per cent of these patients had negative scans and positive x-rays, only three of the lesions in these false-negative scans were active.

Because scanning lacks the obvious

visual clarity of x-ray, interpretation may be difficult when scans are positive and patients have single metastases or such other problems as degenerative joint disease, hyperostosis frontalis interna, and Paget's disease. However, the scan's ability to pick up multiple bony metastatic sites and to locate those missed by x-ray are its outstanding features.

In this series, Dr. Osmond said, there were 131 patients who "demonstrated evidence of bony spread of tumor. Forty-eight of these patients, or 37 per cent of the total number with metastases, had roentgenographic studies that were interpreted as normal. From this same group of 131 patients demonstrating evidence for metastases, 84 patients demonstrated increased information on the scan... a 63 per cent improvement in the sensitivity of detection of metastatic disease."

## In treating cystitis, do you know how to get the best results from Gantrisin® sulfisoxazole/Roche

Economy: Average cost of therapy is still only about 64¢ per tablet.

Recommended adult dosage: 4 to 8 tablets q.i.d. 2 to 4 tablets q.i.d. for children.

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## Britain's NHS at 25: A Matter of Saving the GP

Continued from page 1

into impoverishment. The choice was to enter another specialty or to emigrate."

A single detail may help to highlight his point: a study nine years ago showed that 35 per cent of physicians' offices lacked a washbasin.

How had the service that was launched with such high hopes and genuine social commitment reached this nadir? And how did it make its comeback?

The stability that now prevails may well testify to the system's capacity for accommodating itself to change. It certainly testifies to two other factors—the serious miscalculations made by the founders of the NHS about the cost of a national health care program and the equally serious miscalculations by the profession about the cost of keeping a general practitioner in reasonable financial health.

### Carry Some Useful Lessons

Both points come down to a question of money and carry some useful lessons.

The Beveridge report of 1945, laying the basis for the health service, had estimated that expenditures would run at the sterling equivalent of about \$800,000,000 a year and would remain essentially unchanged for the next 20 years. The reasoning—astounding as it may be in hindsight—was that the costs of health care would go down as the nation's health improved under a comprehensive health care delivery system.

In fact, NHS expenditures rose from about \$300,000,000 in 1948-49, when the service was launched, to more than double five years later—a rise accompanied by the continuing political drumbeat of accusations from the House of Commons that the NHS was riddled with waste and extravagance.

Inflation, of course, accounted for some of the rise, and a growing—rather than declining—popular demand for medical services came into being with the availability of comprehensive care.

The political results of this miscalculation, which had consequences for years to come, were summed up recently by Rudolf Klein, of London's Centre for Studies in Social Policy: "The NHS was [placed] on the defensive. The main anxiety of its administrators seems to have been to protect themselves against the accusation of wasting public money, rather than explore the best ways of spending it."

On its side, the medical profession contributed a formula for paying the general practitioner that was to haunt it for nearly two decades. As a condition for participating in the proposed health service, the profession insisted, and the Government finally agreed, that G.P.s would not be placed on government salary—"We're not civil servants" ran the proud claim—but would become independent contractors, to be paid for the number of their patients annually. In contrast, specialists, hospital staffs, and public health physicians all accepted salaried posts.

### Income Lower Than Others'

Ten years later, if the G.P.s were not going broke, they were overworked, underequipped, and understaffed, and their incomes were certainly not keeping pace with those of other professions.

In settling for a per capita rate of payment, they had also accepted the elimination of fee-for-service or any form of substitute remuneration. The G.P.s had agreed to provide year-round, 24-hour medical care for up to 3,500 patients per doctor. But no provision was made for the differing requirements of a healthy young adult, for example, and an aging couple with chronic ailments; or for complete obstetric services; or for after-hours house calls.

Nor was there any provision for equipment. The physician who wanted to provide a washbasin for his patients did so at his own expense, out of his per

capita fee. From the standpoint of an economy-minded government, this was all to the good.

"The greater your attraction for the patient, or your interest in good medicine, the less money you had," MEDICAL TRIBUNE was told by a B.M.A. leader, who asked not to be identified. "The capitation system was virtually an inducement to poor service."

In retrospect, what is surprising is not that G.P.s began to emigrate but that so few did.

Sir George Godber, chief medical officer of the Department of Health and Social Security, in an interview with MEDICAL TRIBUNE, paid his tribute to the G.P.'s sense of responsibility in those days: "The fact is that the general practitioner, especially at the outset, carried the National Health Service on his shoulders. If he had not been available, the hospital outpatient services would have been swamped. The G.P.s saved the day. They were the key."

By the early '60s it was obvious that the NHS would have to save the G.P. if it was to survive, at least along the ambitious lines that were originally envisioned. A radically revised schedule of fees and allowances, amounting to a virtually new system of payment, was formulated and established through the joint effort of the B.M.A. and the Government.

Per capita payment remained on the heart of the G.P. contract. But this was cushioned by the following additional payments: a basic practice allowance, a basic allowance for "out-of-hours" calls, as well as an extra "out-of-hours" capitation fee for each patient in excess of 1,000 on the G.P.'s list; a larger capitation fee for each patient over age 65; and a basic fee for each patient receiving complete maternity services.

### "Seniority" Allowances Graduated

There were additional allowances for physicians who settled in "underdeveloped" areas or joined group practices, and there were graduated "seniority" allowances for years of service.

Equally important, the G.P. was completely reimbursed for his office rent and taxes and was reimbursed 70 per cent for the money he spent on office staff. If his office was part of his home, he was reimbursed for what it would have cost if he were renting the premises.

How much does this all come to in annual income?

On the British economic graph, the G.P. is doing neither badly nor outstandingly well. Most estimates agree that the British physician's earnings (including those of the specialist and the public health physician) place him in the upper 10 per cent of the population.

But at an average of \$5,750 (\$14,300) net for the general practitioner, and \$7,599 (\$19,000) net annually for a top specialist, it is obvious that the profession is somewhere in the low-middle segment of that 10 per cent.

The B.M.A., which compiled these data, as of April, 1973, stresses that the G.P. has more than doubled his net income since April, 1963, and that the specialist is 71 per cent better off. Further, the rates of increase for doctor's income are in excess of the cost-of-living rises for the same period.

It must be remembered, too, that these figures include only the earnings from fixed government salaries or contracts. Almost all specialists have a roster of private patients, bringing in anywhere from \$5,000 to \$20,000 more per year, and many G.P.s make extra money by contracting to serve as insurance, school, or hotel physicians.

Comparisons with the earnings of physicians in other nations, including those in Western European countries with national health programs of their own, are, in a sense, beside the point. Each system has its own history and its own value systems and has produced its separate allegiances.

"It must be remembered," said Dr. Ernest Colin-Ross, a London general practitioner, "that from most points of view the NHS was an improvement. Most physicians, except for those in fashionable areas, were not making much money in those days. The NHS was also an improvement for the physician who was not good at demanding payment of fees."

As for the present, he added: "I'll be shot for saying this: I don't need more money. I don't need a yacht. On the other hand, my attitude may not be typical."

"Money is not the real issue of contention," said Dr. Dennis Cook, secretary of the Inner London Medical Committee. "Physicians are currently more concerned about the terms of service and the complaint procedures, and the demands upon them, than about their incomes. The majority of physicians are not irked by the incomes they earn. There are 2,000 G.P.s on the list of the inner London Executive Council, and last year only one suffered financial embarrassment."

### Studying Continental Counterparts

On the other hand, there is no doubt that the profession is looking closely at the earnings of its Continental counterparts, especially since Britain's entry into the Common Market. And while strict comparisons are difficult, it would appear that the doctor in other European health insurance programs may be earning more than his British colleague. The reason is held to stem from the fact that all of the European insurance programs are based on one or another form of fee-for-service, rather than capitation. No one here, however, is calling for an end to the capitation system.

As for comparisons with the United States, a fairly prevalent viewpoint was voiced by Dr. James Bramble of Leeds, former head of the militant Young Hospital Staff Physicians and now deputy chairman of the B.M.A.'s Junior Hospital Staff Group Committee.

"I'm not suggesting that we want as much as doctors in the United States," he said. "We don't need that much. We could use more, of course. Chiefly, what we need is a reduction in the pressure on us. You must remember that those of us in my generation have never known a situation of private practice. I think that the majority of us would like to see private practice preserved, mainly as a standard of comparison."

"The NHS is a fantastic boon to the average member of the community. Though our health care may not be as good as some of the very highest practiced in the United States, it is consistently good, immediately available, and strong on rehabilitation."

"The stress is on total care, and treatment by the G.P. or the specialist is only a small part of that concept, especially in cases of chronic illness. The physician is only part of the team, the head chap."

Currently, as Dr. Cook stressed, terms of service are more immediately pressing than problems of money, although that subject is never, of course, far below the surface.

Any discussion of terms of service—meaning largely the rules governing the doctor's obligations to his patients—has to start from the fact that the British G.P. is under contract to provide all "necessary and proper" care for every man, woman, and child on his list.

The contractual commitment is a round-the-clock commitment; the physician is responsible for 24 hours of care a day and must meet that responsibility himself or deputize another physician in his place. The NHS contract provides an allowance for "after hours" deputies.

As a result, Dr. Cook pointed out, the physician is vulnerable to excessive demands from patients, some of whom may consult him more often than their ailments would seem to justify.

"The most common complaint we get,"

he said, "is that the doctor refused to make a home visit. The G.P. has the right to refuse a house call if, in his judgment, it is not warranted. But if it is successfully proved that a visit was called for, the physician is in breach of contract, and subject to a fine—or to a malpractice suit if the patient wants to pursue it that far."

A physician may run into trouble, for example, by reassuring a patient on the phone that his symptoms are probably due to an "upset stomach" when, in fact, a coronary occlusion is in progress.

"The second most common complaint," said Dr. Cook, "is the charge that the doctor failed to examine properly. 'The doctor didn't listen to my story. . . . He gave a prescription without examining me. . . . He stood at the bed and didn't examine me.'"

Under law, a formal complaint must be investigated by the local Executive Council (composed of laymen and physicians) with whom the doctor has his NHS contract. Of 50 complaints investigated in the inner London area last year, Dr. Cook reported, the council decided 12 cases against physicians, finding that they had failed to make house calls that should have been made, or had delayed unreasonably in coming. In a 13th case, the Council agreed with a government complaint that a physician had falsely issued a certificate of illness to a worker who had been absent from his job.

### Problem Not Very Serious

"Is the problem a serious one?" Dr. Cook asked rhetorically. "Not really. Fifty formal complaints a year in an urban area with 2,000 doctors and 3,000,000 patients is a comfortable figure. I myself practiced for 13 years without even knowing the terms of service in my contract. In all of that time there was one complaint against me and that was dismissed."

He added: "The extent of the problem can be seen by the size of the insurance premium to the Medical Defense Union: a general practitioner in Great Britain gets unlimited indemnity for £21 a year [\$52]."

Next article: Emergence of general practice as a status specialty.

## Study Finds No Link Of Coffee Drinking, Myocardial Infarct

Medical Tribune Report

OAKLAND, CALIF.—Available evidence does not support contentions that there is an association between coffee drinking and myocardial infarction, according to the authors of a study at the Kaiser Permanente Medical Care Program here.

Such an association had been found to a study by the Boston Collaborative Drug Surveillance Program, and the authors who reported it in *Lancet* suggested then it might be due to "a substance of substances in coffee other than caffeine."

The authors of the Boston study also cautioned that the association might be based on the fact that "patients who drink [coffee] heavily and patients who develop myocardial infarction have similar personalities, and thus coffee drinking would only be indirectly related to myocardial infarction."

The California Investigators decided there was no association between coffee and myocardial infarction after studying a group of 464 myocardial infarction patients, a group of ordinary controls, and a group of risk controls.

However, an association was found between coffee drinking and cigarette smoking; 34 per cent of the smokers drank more than six cups a day, while only 10 per cent of the nonsmokers drank that much.

The earlier Boston study had also found a strong correlation between coffee drinking and smoking.

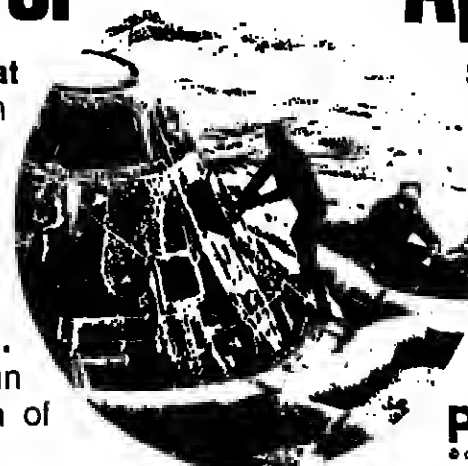
# BETADINE MICROBICIDES

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When potential moon germs were a threat NASA had selected a broad-spectrum BETADINE microbicide for decontamination of the lunar capsules in Apollo 11/12/14 splashdowns.

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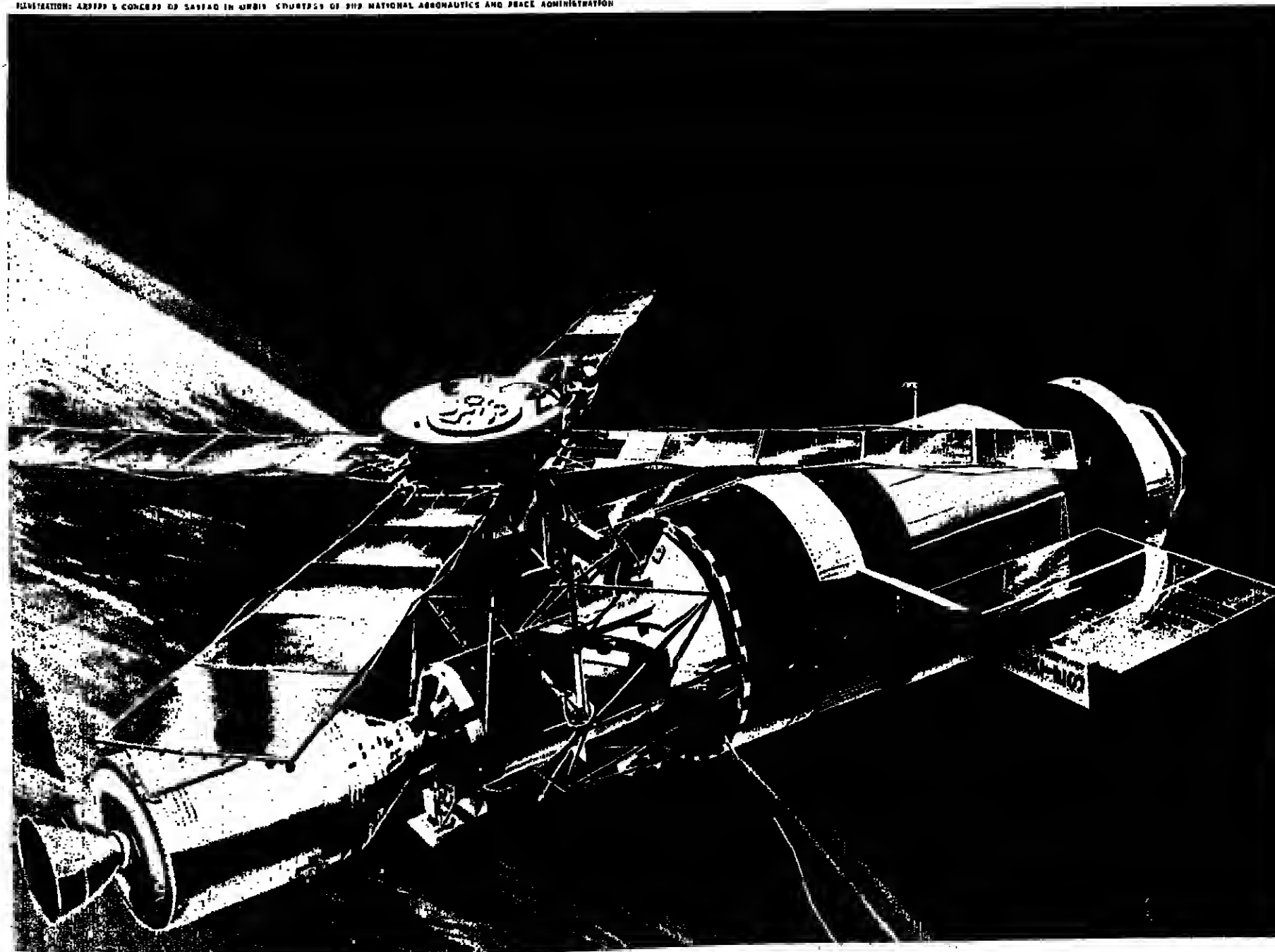
Sky-high microbicidal efficacy plus down-to-earth convenience distinguishes BETADINE antiseptics. They kill bacteria (gram-positive and gram-negative), fungi, viruses, protozoa and yeasts. Yet they are virtually nonstinging, nonirritating and do not stain skin, mucosa, or natural fabrics. And they are available in a variety of forms, designed and formulated for specific uses.

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## Aaron's Physician Proves Good Prophet for Homers

Medical Tribune Report

ATLANTA, GA.—When Henry Aaron of the Atlanta Braves hits his 715th career home run next year, one of the loudest cheers will be from Dr. Robert E. Wells, Atlanta orthopedist and consultant to the Braves and a staunch admirer of the 39-year-old superstar.

Dr. Wells, one of the physicians who treat Hank Aaron, predicted more than a year ago that "Hammerin' Hank" would break Babe Ruth's long-standing major-league record of 714, long considered out of reach. The Babe set that mark 38 years ago.

In an interview with MEDICAL TRIBUNE (June 28, 1972), Dr. Wells said: "Speaking from a medical standpoint and as a baseball fan, I am confident that Hank Aaron will pass Babe Ruth's record. I'll make a guess that Aaron will hit his 715th home run early in 1974."

It is now obvious that Dr. Wells was a good prophet. His patient hit his 713th homer in his next-to-last game this year. "It's hard to think of Hank Aaron as a patient," Dr. Wells said. "He's such an amazing athlete and a tremendous person. He has the body of a man six or eight years younger. As far as his physical condition is concerned, there is no reason why he should stop playing baseball."

### Prediction Was Almost Wrong

"He was hitting home runs at such a fast clip in early and middle August that I thought he might break the record this year. As a matter of fact, I was pulling for him to do it even though it would have made my prediction wrong."

Dr. Wells pointed out that Aaron enjoyed a better year this year than last despite the fact that he played in fewer games. He belted 40 home runs this year, compared with 34 last year. No other 39-year-old player in baseball history has ever done that. Aaron ran up 96 RBIs this year, compared with 77 last, and scored 84 runs, compared with 75. His batting average was .301, against .265. Aaron played in 120 games and missed 42 this year.

"Aaron himself decides whether he is going to play in a particular game," Dr. Wells pointed out. "He rarely plays in a day game after a night game, and he never played in both games of a double-header."

In the 1972 interview with MEDICAL TRIBUNE, Aaron said he would have to stay "free of injuries" to break Ruth's record. "If I can stay healthy," he said, "then I think I can do it."

Fortunately, Aaron has had no serious injuries or illnesses.

Dr. Wells reported that Aaron had "no problem" this year with an old knee injury—a partial tear of a cartilage—which had bothered him in the past.

"Aaron did have some muscular soreness of the upper and lower back, caused by fatigue," the physician related, "but a few days of rest and a little traction and heat straightened that out."

"He had a short episode of intestinal

flu which kept him out of the lineup a few days. He also had stomach cramps for a couple of days while on the West Coast, but doctors who treated him there attributed the cramps to no infection that was going around."

Aaron has had only one fracture in his 20-year career as an outfielder in the National League. That was in his rookie year as a Milwaukee Brave when he broke an ankle. (The Milwaukee Braves became the Atlanta Braves in 1966.)

Dr. Wells said he does not know of any medication that Aaron takes except an occasional aspirin.

"He has no trouble sleeping," the physician said, "if he can get away from the ringing telephone."

Wherever Aaron goes now, he is besieged by autograph seekers, demands for newspaper, TV, and radio interviews, and requests for personal appearances of every kind imaginable. He has managed to stay remarkably cool, calm, and collected.

"Aaron is very stable emotionally," Dr. Wells observed. "He not only gives the external appearance of being a placid man, but he doesn't have any of the physical symptoms that go with emotional disturbances."

Extremely self-disciplined, Aaron has no trouble keeping himself in shape. He avoids eating "too much bread and potatoes" and keeps his weight at about 190 pounds—well distributed on his 6-foot frame. Neither Aaron nor anyone else has noticed any slowing down in his reflexes.

Aaron holds 11 major league and 18 National League hitting records—more than any other player. Aaron and Willie Mays of the New York Mets are the only players to achieve both 600 home runs and 3,000 hits. Aaron leads all other players in history in total bases (6,424) and extra-base hits (2,133).

### Called Consistent, Durable

"A lot of players have hit a lot of home runs for a few years," Dr. Wells commented, "but they haven't had the consistency and durability of Hank Aaron."

At the end of the 1973 season, Aaron said he was "disappointed" that he did not break Ruth's record this year, but he added: "I'm glad that I can look back and feel that I've had a good year." He said he planned to "rest up" and "get lost" for a few days. Aaron, who is divorced, also plans to marry a pretty Atlanta widow, Mrs. Billy Williams.

In the last game of the 1973 season, a crowd of more than 40,600 sat in a steady drizzle and watched Henry Aaron hit three singles and a pop fly—but no home runs. When he took his position in left field for the last time that day, the drenched crowd rose and gave Aaron an ovation that lasted more than five minutes.

Dr. Wells, one of the 40,600 who cheered, called it "one of the most exciting moments I've ever experienced in sports."

## Team Physician at Purdue Calls For National Survey of Sport Injuries

Medical Tribune Report

ATLANTA, GA.—Team physicians, trainers, and coaches should work with epidemiologists to develop a competent, ongoing, nationwide survey of athletic injuries, Dr. Loyal W. Combs, who is the team physician at Purdue University, said here.

Speaking at the 24th annual meeting of the National Athletic Trainers Association, Dr. Combs declared: "It is imperative that we get competent, uniform identification and reporting of sports injuries on a national level."

Dr. Combs said that all interested organizations should pool their money and efforts to develop such a survey.

The Purdue team physician suggested that under a nationwide system of injury reporting, five or six epidemiologists scattered over the country might be designated to collect data concerning athletic injuries.

"They could send this information to a central area where a full-time epidemiologist would computerize and competently analyze all the statistics," Dr. Combs said.



Hank Aaron's 700th home run—July 21.

## IMMATERIA MEDICA

By DUDLEY STRAUS

### The Hurry Condition of Potential Good Samaritans

Forty "unwitting" theological students at Princeton University were subjected to an experimental situation, according to a release from the American Psychological Association, and we've been trying to decide what grabs us the most—the experiment, its language, or the investigators' arithmetic.

These 40 ministers-to-be were asked to prepare a short talk either on the parable of the good Samaritan or on vocations. They then were given a campus map with specific directions for reaching a laboratory where the speech was to be taped.

The "subjects" were told they were already late for the session (high-hurry condition), were expected momentarily (intermediate-hurry condition), or that they could take their time (low-hurry condition).

Along their way was the booby trap—a groaning, coughing person slumped in a doorway. Sixteen of the subjects stopped to help the "victim," the report says; of these, "63 per cent were low-hurry subjects; 45 per cent were intermediate-hurry subjects; 10 per cent were high-hurry subjects."

(As we work that out, we get a total of 118 per cent, and we also get 10.08 divinity students in a low hurry, 7.2 in an intermediate hurry, and 1.6 in a high hurry.)

The investigators conclude that "the hurry condition of the subject proved significant to whether he would stop to help the victim." They also observe that "the lowly Samaritan, on the other hand, with little responsibility and time on his hands, could afford to stop and assist the distressed victim."

We have an enormous store of brilliant comments to offer on this study, but our hurry state is penking, so desperate readers will just have to get along without them.

We had just learned, from the St. Louis County Medical Society Bulletin, of the existence of the American Trauma Society when we received a release from the Veterans Administration reporting a program that "provides veterans who are dropouts from the human race an opportunity to complete college preparatory courses."

We assume they were suffering from the American trauma and hope that the society will get in touch with them about it.

"What is your diagnosis—psycho-physio-offer cerebral angiography and replace the Medrad injector and utilizes a film—various tranquilizers and mood elevators? Have you ever tried referring such a patient to Alanon? In Alanon, instead of taking pills and blaming her troubles on her husband, a woman can learn how to cope with life and how to be happy in spite of her husband's alcoholism—whether he quits drinking or not. Alanon groups are composed of the spouses and other relatives and friends of alcoholics."

—Bulletin of the Orange County (Calif.) Medical Association.

Thanks for the tip, but the diagnosis is going to take a bit longer than you might have thought.

Readers are invited to contribute items of 100 words or less to this column. Contributions should be mailed to MEDICAL TRIBUNE, 880 Third Avenue, New York, N.Y., 10022.

Preventing Emergency Calls #1

# Toys can be DANGEROUS

With the Christmas toy shopping season here, both physicians and parents should be aware that toys—no matter how innocent they look—can be dangerous. In fiscal year 1973 nearly 515,000 injuries associated with toys, tricycles, and bicycles were treated in hospital emergency rooms alone. A poorly designed toy—or a toy in the hands of a child too young to handle it—can cause permanent injury or death, warns the U.S. Consumer Product Safety Commission. The commission has the power to ban toys with mechanical, electrical, or thermal hazards and has banned some 1,500 individual toys (a list of the banned toys is available through any CPSC area office). In addition, the commission recommends that certain common sense rules be followed in selecting toys and that parents instruct their children in the proper usage of their toys.



Certain toys, such as chemistry sets and electrical toys, should be brought only for more mature children. A young child might open a bottle in a chemistry set with his mouth.



Darts are no longer sold as toys. However, they are still carried as sporting goods. Both darts and arrows should be played with only under the supervision of an adult.



Toys with small parts should be avoided for infants and toddlers. And parents should be aware that a toy bought for an older child may fall into the hands of a younger one. Fabrics on toys should be labeled nonflammable, washable, and hygienic.



Toy pistol caps that exceed a sound level of 158 db. are banned. No cap should be fired within a foot of ear.



Dr. Robert J. Izant, Jr., of Cleveland's University Hospitals, has studied bicycle injuries and found that many occur when two children attempt to ride the same bike.



### Physicians:

We will supply free two-color reprints of this poster, suitable for office display. Send your request to DANGEROUS TOYS, c/o Medical Tribune, 880 Third Avenue, New York, N.Y. 10022. Please specify the number of posters you would like and include 25¢ for postage and handling (Tape quarter to a card.)

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